Medtronic

Clinical Investigation Plan Title	STOP AF First
Clinical Investigation Plan Identifier	MDT16012AFS001
Study Product	Arctic Front Advance™ Cardiac CryoAblation Catheter
Application Number	IDE #G1160219
ClinicalTrials.gov Identifier	NCT03118518
Sponsor	Medtronic 8200 Coral Sea St NE Mounds View, MN 55112
Document Title	STOP AF First Clinical Investigation Plan
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Clinical Investigation Plan

Clinical Investigation Plan/Study Title	STOP AF First
Clinical Investigation Plan Identifier	MDT16012AFS001
Study Product Name	Arctic Front Advance™ Cardiac CryoAblation Catheter
Sponsor/Local Sponsor	United States of America Medtronic, Inc. 8200 Coral Sea St NE Mounds View, MN U.S.A. 55112 Europe Medtronic, Bakken Research Center B.V. Endepolsdomein 5 6229 GW Maastricht The Netherlands
Document Version	Version 5.0, 05DEC2017
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1. Version History

Version	Summary of Changes	Author(s)/Title
1.0	Initial Release	Kirsten Rasmussen, Clinical Research Specialist Chris Anderson, Sr. Statistician
2.0	Section 1- Added local sponsor contact information for Europe, added coordinating investigators	Kirsten Rasmussen, Clinical Research Specialist Chris Anderson, Sr. Statistician
2.0	Section 2, Glossary- Added additional terms	Kirsten Rasmussen, Clinical Research Specialist Chris Anderson, Sr. Statistician
2.0	Section 3, Synopsis- Updated to include Europe, added sections to comply with ISO 14155, modified to reflect all other changes throughout document.	Kirsten Rasmussen, Clinical Research Specialist Chris Anderson, Sr. Statistician
2.0	Section 4.2, Purpose- Added EU indication	Kirsten Rasmussen, Clinical Research Specialist Chris Anderson, Sr. Statistician
2.0	Section 5, Objectives and Endpoints- All objectives and endpoints were modified based on new randomized study design.	Kirsten Rasmussen, Clinical Research Specialist Chris Anderson, Sr. Statistician
2.0	Section 6, Study Design- Updated to a randomized study design with increased sample size and sites in Europe. Modified rationale to support the new primary objectives.	Kirsten Rasmussen, Clinical Research Specialist Chris Anderson, Sr. Statistician
2.0	Section 7, Product Description- Added device information specific to EU, added additional detail for ISO 14155 compliance	Kirsten Rasmussen, Clinical Research Specialist Chris Anderson, Sr. Statistician
2.0	Section 8, Investigator Center Selection- Added section for ISO 14155 compliance	Kirsten Rasmussen, Clinical Research Specialist Chris Anderson, Sr. Statistician
2.0	Section 9, Center Activation- Added section for ISO 14155 compliance	Kirsten Rasmussen, Clinical Research Specialist Chris Anderson, Sr. Statistician

Version	Summary of Changes	Author(s)/Title
2.0	Section 10, Selection of Subjects- Modified the first Inclusion Criteria per FDA feedback "A diagnosis of symptomatic paroxysmal AF with the following documentation: (1) physician's note indicating recurrent self- terminating AF or paroxysmal AF; and (2) any ECG documented AF within 6 months prior to enrollment. " Exclusion criteria- changed 3 months and 6 months to 90 days and 180 days for clarity.	Kirsten Rasmussen, Clinical Research Specialist Chris Anderson, Sr. Statistician
2.0	Section 11.1, Study Procedures, Schedule of Events- Added randomization, treatment arm, reablation/crossover ablation requirements, pregnancy screen, chest x-ray for phrenic nerve injury, MRI or CT scan for suspected PV stenosis, health care utilization data collection. Changed QOL screening from SF-12 to EQ-5D. Changed Holter to "continuous ambulatory ECG monitoring."	Kirsten Rasmussen, Clinical Research Specialist Chris Anderson, Sr. Statistician
2.0	Section 11.2, Study Procedures, Medications- Added control arm medication requirements and more detailed anticoagulation requirements.	Kirsten Rasmussen, Clinical Research Specialist Chris Anderson, Sr. Statistician
2.0	Section 11.3, Study Procedures, Subject Consent- Updated to add EU and for ISO 14155 compliance.	Kirsten Rasmussen, Clinical Research Specialist Chris Anderson, Sr. Statistician
2.0	Section 11.4, Study Procedures, Randomization and Treatment Assignment- Modified from single arm study to randomized study.	Kirsten Rasmussen, Clinical Research Specialist Chris Anderson, Sr. Statistician

Version	Summary of Changes	Author(s)/Title
2.0	Section 11.5, Study Procedures, Description of All Study Procedures and Visits- Updated per Section 11.1, Schedule of Events, added antiarrhythmic drug arm requirements, modified anticoagulation and TEE requirements, updated phrenic nerve injury screening requirements, added assessment of whether neurological evaluation is required at hospital discharge, changed six week phone/office visit to one month office visit and added additional requirements to the visit, changed Holter requirement to a general term "24 hour continuous monitoring," describe the 24 hour continuous monitoring and patient activated ECG data collection.	Kirsten Rasmussen, Clinical Research Specialist Chris Anderson, Sr. Statistician
2.0	Section 11.10, Subject Withdrawal or Discontinuation- Updated reasons for withdrawal	Kirsten Rasmussen, Clinical Research Specialist Chris Anderson, Sr. Statistician
2.0	Section 12, Risks and Benefits- Added risks per FDA feedback	Kirsten Rasmussen, Clinical Research Specialist Chris Anderson, Sr. Statistician
2.0	Section 13, Adverse Event Assessments- Added antiarrhythmic drug related category and ISO 14155 requirements.	Kirsten Rasmussen, Clinical Research Specialist Chris Anderson, Sr. Statistician
2.0	Section 15, Statistical Design and Methods- Updated based on modified objectives and endpoints.	Kirsten Rasmussen, Clinical Research Specialist Chris Anderson, Sr. Statistician
2.0	Section 16, Ethics- Updated to include Europe and ISO 14155 regulations.	Kirsten Rasmussen, Clinical Research Specialist Chris Anderson, Sr. Statistician
2.0	Section 17, Study Administration- Updated to include Europe and ISO 14155 regulations.	Kirsten Rasmussen, Clinical Research Specialist Chris Anderson, Sr. Statistician
3.0	Changed "Objective Performance Criteria" to "Performance Goal" in Section 2, Glossary, and Sections 15.2.4 and 15.2.6 in the Statistical Design and Methods section.	Kirsten Rasmussen, Clinical Research Specialist Chris Anderson, Sr. Statistician

Version	Summary of Changes	Author(s)/Title
3.0	Updated the following sections to change the 30 day AAD optimization period to a 90 day AAD optimization period: 3.0, Synopsis, 6.0, Figure 1, Study Design Table, 11.1, Schedule of Events, and 5.1.4.1, Primary Efficacy Endpoint, 11.5.8, Scheduled Follow-up Visits, 15.1.2, Endpoint Definition	Kirsten Rasmussen, Clinical Research Specialist Chris Anderson, Sr. Statistician
3.0	Added the following statement to the medication sections: The 2014 AHA/ACC/HRS Guideline for the Management of Patients with Atrial Fibrillation should be consulted for AAD prescriptions. (Sections 11.2, 11.5.2, and 11.5.5)	Kirsten Rasmussen, Clinical Research Specialist Chris Anderson, Sr. Statistician
4.0	Edited two exclusion criteria: 1) changed the BMI value from >35 to >40; 2) added "severe" prior to obstructive sleep apnea.	Mindy Hoey, Prin. Clinical Research Specialist Chris Anderson, Sr. Statistician
5.0	Updated contact information in Table 1 and Table 2 for new study personnel and CRO	Jen Diouf, Sr. Clinical Research Specialist Chris Anderson, Sr. Statistician
5.0	Changed the reduction in diameter of the pulmonary vein analysis categories cutoff from 75% to 70% in the synopsis as well as sections 5.1.4.2 and 15.4.2.1	Jen Diouf, Sr. Clinical Research Specialist Chris Anderson, Sr. Statistician
5.0	Edited two exclusion criteria: 1) exclusion criteria of prior persistent AF to exclude the reference to cardioversion after 48 hr to reflect the updated definition in the 2017 HRS/EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation; 2) removed BMI exclusion criteria	Jen Diouf, Sr. Clinical Research Specialist Chris Anderson, Sr. Statistician
5.0	Edited Section 11.1.1 to include additional modes of data collection: direct to patient contact and remote technology transmissions/uploads	Jen Diouf, Sr. Clinical Research Specialist Chris Anderson, Sr. Statistician

Version	Summary of Changes	Author(s)/Title
5.0	Updated Section 11.5.1 to allow data collection performed as part of routine clinical evaluations within 30 days prior to the date the subject signed the Informed Consent Form: physical examination, CHA2DS2-VASc Score, 12 lead ECG, Demographics, Medical History	Jen Diouf, Sr. Clinical Research Specialist Chris Anderson, Sr. Statistician
5.0	Updated Section 11.5.3.2 to refer to the updated 2017 HRS/EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation for anticoagulation recommendations	Jen Diouf, Sr. Clinical Research Specialist Chris Anderson, Sr. Statistician
5.0	In Section 12.1 an additional risk, infection (e.g. sepsis) was added in response to a labeling update for the ArcticFront Advance and the pneumothorax risk is moved to the alphabetical location. In addition, language was included to account for the identification of additional risks.	Jen Diouf, Sr. Clinical Research Specialist Chris Anderson, Sr. Statistician
5.0	Adverse event relatedness definitions (not related, possibly related, causal relationship) were added in section 13.1	Jen Diouf, Sr. Clinical Research Specialist Chris Anderson, Sr. Statistician
5.0	Section 15.1.6 was corrected to state that sample size assumptions were calculated using the two-sided chi-squared test	Jen Diouf, Sr. Clinical Research Specialist Chris Anderson, Sr. Statistician
5.0	Section 15.4.5.2 was updated to remove the plan to describe the nature and duration of arrhythmia	Jen Diouf, Sr. Clinical Research Specialist Chris Anderson, Sr. Statistician
5.0	Appendix D and E were updated to note that the list of participating Investigators and institutions as well as a final IRB list will be distributed under separate cover	Jen Diouf, Sr. Clinical Research Specialist Chris Anderson, Sr. Statistician
5.0	Corrected ISO 14155 reference in sections 7.13 and 16.1	Jen Diouf, Sr. Clinical Research Specialist Chris Anderson, Sr. Statistician
5.0	In Section 7.6 Added that the most current market approved software version available will be used at the site for the CryoCath Cryoablation Console.	Jen Diouf, Sr. Clinical Research Specialist Chris Anderson, Sr. Statistician

Version	Summary of Changes	Author(s)/Title
5.0	Added wording in Section 17.2 to confirm that the maintenance and calibration or study devices will be monitored.	Jen Diouf, Sr. Clinical Research Specialist Chris Anderson, Sr. Statistician
5.0	Included wording in Section 12 to address the potential risks, potential benefits and risk-benefit rationale for the control group.	Jen Diouf, Sr. Clinical Research Specialist Chris Anderson, Sr. Statistician

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Sponsor Contact information

Medtronic contact information is provided in Table 1. This information is subject to change during the course of the clinical study. Periodic updates to study contact information will be sent to the centers as needed.

Table 1: Study sponsor and monitoring contact information

Study sponsors and contacts
Worldwide and US Clinical Study Leader Jen Diouf, Senior Clinical Research Specialist [redacted] *Europe* Daniel Becker, Principal Clinical Research Specialist [redacted]
Monitoring contacts
Ian Schorn, Medical Research Manager, Clinical [redacted]

Contract Research Organizations

Changes to Table 2 will be provided under a separate cover.

Table 2: CRO information

Contact Information	Duties performed
NAMSA 400 Highway 169 South, Suite 500 Minneapolis, MN 55426 [redacted]	• Database development, data review and SAS programming • Site monitoring activities • Clinical safety management and potential complaint reporting • Clinical Events Committee management
HeartCor Solutions, LLC 2403 Harnish Drive, Suite 201 Algonquin, IL 60102 [redacted]	• Distribution of equipment for rhythm monitoring. • Adjudication of atrial arrhythmias.

Steering Committee

Changes to Table 3 will be provided under a separate cover.

Table 3: Steering Committee contact information

Committee Member	Contact information
Oussama Wazni, MD	Cleveland Clinic 9500 Euclid Avenue, Cleveland, OH 44195 [redacted] Professional Position: Staff Cardiologist, Section of Cardiac Electrophysiology and Pacing, Department of Cardiovascular Medicine; Clinical Assistant Professor of Medicine
Gopi Dandamudi, MD	Indiana University Krannert Institute of Cardiology 1801 N. Senate Blvd, Suite 4000, Indianapolis, IN 46202 [redacted] Professional Position: Cardiac Electrophysiology and Assistant Professor of Medicine
Steven Nissen, MD	Cleveland Clinic 9500 Euclid Avenue, Cleveland, OH 44195 [redacted] Professional Position: Staff Cardiologist, Professor of Medicine

2. Glossary

Term	Definition
AE	Adverse event
AF	Atrial fibrillation
AAD	Antiarrhythmic drug
ACC	American College of Cardiology
ACT	Activated clotting time
ADE	Adverse device effect
AFL	Atrial flutter
AHA	America Heart Association
AT	Atrial tachycardia
AFEQT	Atrial Fibrillation Effect on QualiTy-of-life Questionnaire
BMI	Body mass index
C	Celsius
CA	Competent Authority
CEC	Clinical Events Committee
CFR	Code of Federal Regulations
CIP	Clinical investigation plan
CRF	Case report form
CTA	Clinical trial agreement
DD	Device deficiency
e.g.	For example

Term	Definition
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EQ-5D	EuroQol 5 Dimensions Questionnaire
F	Fahrenheit
FAL	Foreseeable adverse event list
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
GEE	Generalized estimating equation
HCU	Health Care Utilization
HIPAA	Health Insurance Portability and Accountability Act
HRS	Heart Rhythm Society
IC	Informed Consent
ICF	Informed Consent Form
ID	Identification
IDE	Investigational device exemption
Inc	Incorporated
INR	International normalized ratio
IRB	Institutional review board
LVEF	Left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
NOAC	Novel oral anticoagulant
NYHA	New York Heart Association

Term	Definition
N2O	Nitrous Oxide
PG	Performance Goal
PV	Pulmonary vein
PAF	Paroxysmal atrial fibrillation
PCI	Percutaneous coronary intervention
PVI	Pulmonary vein isolation
PTCA	Percutaneous transluminal coronary angioplasty
QoL	Quality of Life
RF	Radiofrequency
RI	Right inferior
RS	Right superior
SD	Standard deviation
SAE	Serious adverse event
SAP	Statistical analysis plan
SCD	Sudden cardiac death
SADE	Serious adverse device effect
SR	Sinus Rhythm
TEE	Transesophageal echocardiogram
TIA	Transient ischemic attack
TTE	Transthoracic echocardiogram
US	United States
UADE	Unanticipated adverse device effect

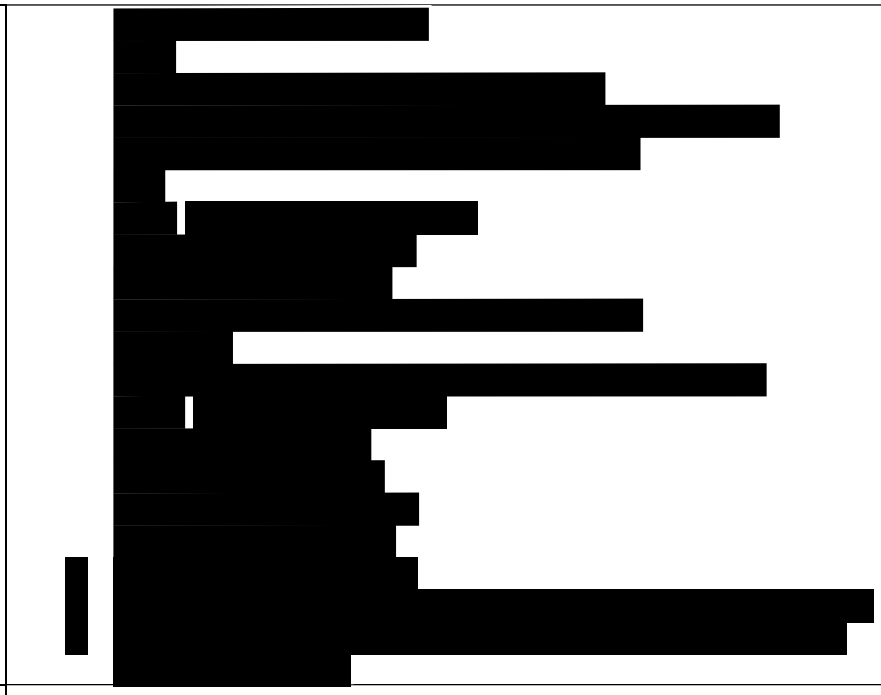
3. Synopsis

Title	STOP AF First
Clinical Study Type	Pivotal (US)/ Post-market interventional (Europe)
Product Name	Arctic Front Advance™ Cardiac CryoAblation Catheter
Sponsor	United States of America Medtronic, Inc. 8200 Coral Sea St NE Mounds View, MN U.S.A. 55112
Local Sponsor	Europe Medtronic, Bakken Research Center B.V. Endeplosdomein 5 6229 GW Maastricht The Netherlands
Indication Under Investigation	Current indication in the US: The Arctic Front Advance™ Cardiac CryoAblation Catheter is indicated for the treatment of *drug refractory* recurrent symptomatic paroxysmal atrial fibrillation. Indication under investigation for the US: The Arctic Front Advance™ Cardiac CryoAblation Catheter is indicated for the treatment of recurrent symptomatic paroxysmal atrial fibrillation. The indication under investigation is within the approved indication in Europe.
Investigation Purpose	The purpose of the study is to provide data demonstrating the safety and effectiveness of the Arctic Front Advance™ Cardiac CryoAblation Catheter for the treatment of recurrent symptomatic paroxysmal AF, without the requirement that the subjects be drug refractory.
Product Status	The Arctic Front Advance™ Cardiac CryoAblation Catheter is market released and will become investigational when used as indicated in the study in the US. The catheter is market released and will be used within the approved indications in Europe, therefore is not considered investigational for the intended patient population in Europe.
Primary Objective	Primary Efficacy Objective: Demonstrate the superiority of cryoballoon ablation as compared to antiarrhythmic drug (AAD) therapy in terms of the rate of freedom from AF/AT/AFL in a non-drug refractory paroxysmal AF population.

	Primary Safety Objective: Demonstrate an acceptable safety profile of the cryoballoon ablation procedure as a first line therapy in a non-drug refractory paroxysmal AF population.
Secondary Objectives	Secondary Objectives are as follows: 1. Assess changes in quality of life (QoL) between baseline and 12 months in the cryoballoon ablation arm. 2. Compare health care utilization (HCU) between the treatment and control arms.
[redacted]	[redacted]

Primary Endpoint	Primary Efficacy Endpoint:
	
	The primary endpoint is treatment success at 12 months after AAD initiation (control arm) or after the pulmonary vein isolation ablation procedure utilizing the Arctic Front Advance™ Cardiac CryoAblation Catheter (treatment arm). A treatment success is the opposite of a treatment failure.
	
	Treatment failure is defined as any of the following components:
	
	• Acute procedural failure (treatment arm only)
	• Documented AF/AT/AFL on ambulatory monitoring/12-lead ECG after the 90 day post-ablation blanking period (treatment arm)/AAD optimization period (control arm)
	  ○ Minimum of 30 seconds on ambulatory monitoring or 10 seconds on 12-lead ECG.
	  ○ Note: Documented occurrence and treatment of typical right-sided cavotricuspid isthmus dependent atrial flutter is not considered a failure if confirmed by entrainment maneuvers during EP testing.
	• Any subsequent AF surgery or ablation in the left atrium.
	• Any subsequent cardioversion after the 90 day post-ablation blanking period (treatment arm)/AAD optimization period (control arm).
	• Class I or III antiarrhythmic drug (or sotalol) use after the 90 day blanking period (treatment arm only).
	
	The AAD optimization period is defined as the first 90 days after AAD initiation (control arm). The post-ablation blanking period is defined as the first 90 days after the index ablation procedure (treatment arm).

	Recurrences of atrial arrhythmias during the AAD optimization/blanking periods will not be counted in the determination of the first clinical failure for the primary endpoint. Within the AAD optimization period/post-ablation blanking period, recurrent arrhythmias can be managed with medications or cardioversions. Reablation will be considered a primary endpoint failure at all times, including during the 90 day post-ablation blanking period. Acute procedural failure (treatment arm only) is defined as: a) Inability to isolate all accessible targeted pulmonary veins (assessed for entrance block and, where assessable, exit block) during the index ablation procedure. b) Left atrial non-PVI ablations including but not limited to, ablation of linear lesions c) Use of a non-study device in the left atrium. <u>Primary Safety Endpoint:</u> The following adverse events will be counted towards the primary safety endpoint: • Transient Ischemic Attack (TIA)within 7 days • Cerebrovascular accident within 7 days • Major bleeding that requires transfusion or results in a 20% or greater fall in hematocrit (HCT) within 7 days • Development of a significant pericardial effusion within 30 days. A significant pericardial effusion is one that results in hemodynamic compromise, requires elective or urgent pericardiocentesis, or results in a 1-cm or more pericardial effusion as documented by echocardiography. • Symptomatic PV stenosis within 12 months; accompanied by one of the following: 50%-70% reduction in diameter of the pulmonary vein, with symptoms not explained by other conditions; OR >70% reduction in diameter of the pulmonary vein • MI within 7 days • PNI unresolved at 12 months • AE fistula within 12 months • Major vascular complication that requires intervention, prolongs the hospital stay, or requires hospital admission (within 7 days).
Secondary Endpoints	1. The difference in composite scores from the AFEQT questionnaire taken at baseline and 12 month visits, and the difference in composite scores for the EQ-5D questionnaire taken at baseline and 12-month visits. 2. 12-month rates of cardiovascular HCU events, and 12-month rates of cardioversion (either electrical or pharmacological).
[redacted]	[redacted]

	
Study Design	Prospective, interventional, multi-center, randomized, controlled, unblinded clinical study. The study will be conducted at up to 30 sites in the US and up to 10 in Europe.
Study Duration	All randomized study subjects will be followed from the time of consent through 12 months post-index cryoballoon ablation procedure (treatment arm), or AAD initiation (control arm). Subjects will be exited from the study at the conclusion of the 12 month follow-up visit. The expected total study duration is approximately 30 months, representing 18 months of enrollment and 12 months of subject follow-up.
Sample Size	210 enrolled subjects in the US and Europe.
Inclusion/Exclusion Criteria	The following is a list of inclusion/exclusion criteria: <u>Inclusion criteria</u> • A diagnosis of symptomatic paroxysmal AF with the following documentation: (1) physician's note indicating recurrent self-terminating AF or paroxysmal AF; and (2) any ECG documented AF within 6 months prior to enrollment. • Age 18-80 <u>Exclusion criteria</u>

	• History of AF treatment with class I or III antiarrhythmic drug, including sotalol, with the intention to prevent an AF recurrence. However, patients pretreated with above AAD for less than 7 days with the intention to convert an AF episode are allowed. • Prior persistent AF (continuous AF that is sustained >7 days) • Left atrial diameter greater than 5.0 cm • Prior left atrial ablation or left atrial surgical procedure • Presence or likely implant of a permanent pacemaker, biventricular pacemaker, loop recorder, or any type of implantable cardiac defibrillator (with or without biventricular pacing function) • Presence of any pulmonary vein stents • Known presence of any pre-existing pulmonary vein stenosis • Pre-existing hemidiaphragmatic paralysis • Presence of any cardiac valve prosthesis • Moderate or severe mitral valve regurgitation or stenosis • Any cardiac surgery, myocardial infarction, PCI / PTCA or coronary artery stenting which occurred during the 90 day interval preceding the date the subject signed the Informed Consent Form • Unstable angina • NYHA class III or IV congestive heart failure and/or known left ventricular ejection fraction (LVEF) less than 45% • Diagnosis of primary pulmonary hypertension • Rheumatic heart disease • Thrombocytosis, thrombocytopenia • Contraindication to anticoagulation therapy • Active systemic infection • Hypertrophic cardiomyopathy • Cryoglobulinemia • Known reversible causes of AF, including but not limited to uncontrolled hyperthyroidism, severe obstructive sleep apnea, and acute alcohol toxicity. • Any cerebral ischemic event (strokes or TIAs) which occurred during the 180 day interval preceding the date the subject signed the Informed Consent Form, or any known unresolved complications from previous stroke/TIA • Existing thrombus • Pregnancy • Patient with life expectancy that makes it unlikely 12 months of follow-up will be completed. • Current or anticipated participation in any other clinical trial of a drug, device or biologic during the duration of this study not pre-approved by Medtronic • Patients with contraindications to a Holter monitor • Unwilling or unable to comply fully with study procedures and follow-up

Study Procedures and Assessments	Subjects in the treatment arm will undergo a pulmonary vein isolation (PVI) ablation procedure with the Arctic Front Advance™ Cardiac CryoAblation Catheter. Subjects in the control arm will be treated with an antiarrhythmic drug as prescribed by the study investigator. Subjects will have follow-up visits at 1, 3, 6, and 12 months post-AAD initiation or ablation. Subjects will be exited at the conclusion of the 12 month visit.
Safety Assessments	Adverse event data collection will begin once subjects sign the Informed Consent Form and will continue through study exit. For the purposes of the study, the following Adverse Events will be collected: • All procedure related AEs • All cryoablation system related AEs • All AAD related AEs • All cardiovascular related AEs • All Serious Adverse Events (SAEs), regardless of relatedness

4. Introduction

4.1. Background

Atrial Fibrillation (AF) is a common and disabling cardiac arrhythmia with a heterogeneous clinical presentation. The fundamental pathophysiology consists of atrial wavelets propagating in different directions, causing disorganized atrial depolarization without effective atrial contraction, with concomitant rapid and irregular ventricular contractions. AF can be clinically stratified based on whether episodes are self-terminating (paroxysmal) or persistent. Paroxysmal AF (PAF) is defined as recurrent AF that terminates spontaneously or with intervention within 7 days of onset. Persistent AF is defined as continuous AF that is sustained beyond 7 days (Calkins, et. al. 2017).

AF is the most common of the sustained arrhythmias affecting millions of people worldwide. In the US, AF affects between 2.7 million and 6.1 million adults (January, Wann, et al. 2014), and that number is expected to double over the next 25 years (Go, et al. 2001). Prolonged AF may lead to electrical, mechanical, and structural changes to the left atrium, which may then progress to tachycardia-induced cardiomyopathy, heart failure and persistent AF. The prognosis is related to the underlying cause of the disease, with idiopathic causes having the best prognosis and ischemic cardiomyopathy having a poor prognosis. The mortality rate in patients with AF is twice that of patients without AF and the risk of AF-related stroke is 5-fold compared to the risk in patients without AF (Wolf, Abbott and Kannel 1991).

In the US, approved treatment options for newly diagnosed symptomatic paroxysmal AF are limited to pharmaceutical therapy because the labeling of cardiac ablation catheters is for "drug refractory" patients. Patients must be refractory or intolerant to at least 1 class I or III antiarrhythmic drug (AAD)

before ablation may be attempted. Pharmacological therapy for AF (paroxysmal and persistent) has limited antiarrhythmic efficacy, with recurrence of AF reported at 44% to 67% within one year, based on a systematic review of 45 randomized controlled clinical trials (Lafuente-Lafuente, Mouly, et al. 2006). Treatment with AADs may also result in an increased risk for adverse events. Results of an AFFIRM sub study showed that adverse events resulting in discontinuation of the treatment were common for AADs, occurring in 11.1% to 28.1% of patients, depending on the AAD used (AFFIRM First Antiarrhythmic Drug Substudy Investi. 2003). The RAAFT-2 study found that AAD's had a success rate of 42% at one year in 61 previously treatment-naive paroxysmal AF patients; meanwhile, the 2014 AHA/ACC/HRS guideline for the management of patients with AF stated that "much like other antiarrhythmic drugs, with the exception of amiodarone, the rates of maintaining sinus rhythm at 1 year for sotalol are 30 -50%" (January et. al. 2014) (Morillo, et al. 2014).

Atrial fibrillation is known to cause electrical remodeling of the atria as well as structural changes that promote perpetuation and progression of symptoms (Wijesurendra and Casadei 2015) (Shulka and Curtis 2014) (Jalife and Kaur 2015). Untreated PAF can give rise to persistent or permanent forms of the disease (De Vos, et al. 2010), which may be more resistant to contemporary AF treatments (Oral, et al. 2002) (Romero, et al. 2015). As such, early and effective intervention is key for normalizing sinus rhythm (SR) and preventing further remodeling and disease progression (Nattel, et al. 2014) (Cosio, et al. 2008). AAD treatments have little to no effect on remodeling (Nattel, et al. 2014) and although may restore SR in the short-term, have high long-term relapse rates (45-90%) (Cosio, et al. 2008) making this treatment largely ineffective at preventing progression of AF. By contrast, early evidence seems to indicate that catheter ablation may reverse indicators of structural remodeling associated with AF (Walters, et al. 2016) (Wu, et al. 2016). Furthermore, catheter ablation, particularly using the Arctic Front Advance™ Cardiac CryoAblation Catheter, hereafter also referred to as the cryoballoon, has a much higher efficacy rate and may be even more effective when provided earlier after AF onset (Arena, et al. 2016) (Tanner, et al. 2011).

Catheter ablation treatment strategies for AF have evolved over time and currently include pulmonary vein isolation (PVI) as a cornerstone of ablation therapy in all types of AF (paroxysmal and persistent) (Raviele 2012) (Jais, et al. 2006). AF arises primarily from the left side of the heart in (or near) the atrium, particularly where the pulmonary veins (PVs) join the atrium. The fundamental basis for the AF ablation procedure is the creation of myocardial lesions that block the propagation of AF wave fronts from the triggering source. The muscular sleeves within the PVs have been established as a critical source of AF triggers (Caulkins and et. al. 2007).

The safety profile of cryoballoon ablation is also well established. The STOP AF trial (Packer, et al. 2013) was a prospective, multicenter, randomized, controlled investigation device exemption (IDE) study designed to compare outcomes of cryoballoon and antiarrhythmic drug therapies in patients with PAF. Six point one percent (6.1%) of cryoballoon subjects experienced a procedure-related event or major adverse event versus 8.5% of AAD subjects. An analysis of 149 cryoballoon studies with 11,242 patients (see Appendix A for literature search methodology) showed similar complication rates to STOP AF.

The STOP AF Post Approval Study was designed to provide long-term safety and effectiveness of the Arctic Front and Arctic Front Advance™ Cardiac Cryoablation Catheter System, including the Freezor® MAX Cardiac cryoablation catheter according to the Product Labeling. Inexperienced users were selected as study Investigators in order to understand complication rates in a real world setting. There were 402 subjects enrolled. The study is currently in the follow-up phase, with all enrolled subjects having been followed for one year post-ablation procedure. Major procedure related events occurred in 20/341 patients (5.9% of patients and 5.7% of procedures). No device or procedure related deaths were reported (Knight, et al. 2016).

4.2. Purpose

The purpose of the STOP AF First study is to provide data demonstrating the safety and effectiveness of the Arctic Front Advance™ Cardiac CryoAblation Catheter for the treatment of recurrent symptomatic paroxysmal AF, without the requirement that subjects be drug refractory. The current indication is the US is as follows: The Arctic Front Advance™ Cardiac CryoAblation Catheter is indicated for the treatment of *drug refractory* recurrent symptomatic paroxysmal atrial fibrillation. The proposed indication in the US is as follows: The Arctic Front Advance™ Cardiac CryoAblation Catheter is indicated for the treatment of recurrent symptomatic paroxysmal atrial fibrillation. The proposed indication is within the approved indications for use in Europe.

5. Objectives and Endpoints

5.1. Objectives

5.1.1. Primary Objective(s)

5.1.1.1. Primary Efficacy Objective

Demonstrate the superiority of cryoballoon ablation as compared to AAD therapy in terms of the rate of freedom from AF/AT/AFL in a non-drug refractory paroxysmal AF population.

5.1.1.2. Primary Safety Objective

Demonstrate an acceptable safety profile of the cryoballoon ablation procedure as a first line therapy in a non-drug refractory paroxysmal AF population.

5.1.2. Secondary Objectives

Secondary Objectives are as follows:

1. Assess changes in quality of life between baseline and 12 months in the cryoballoon ablation arm.
2. Compare health care utilization between the treatment and control arms.

5.1.3. [redacted]

5.1.4. Primary Endpoint

5.1.4.1. Primary Efficacy Endpoint

The primary endpoint is treatment success at 12 months after AAD initiation (control arm) or after the pulmonary vein isolation ablation procedure utilizing the Arctic Front Advance™ Cardiac CryoAblation Catheter (treatment arm). A treatment success is the opposite of a treatment failure.

Treatment failure is defined as any of the following components:

a) Acute procedural failure (treatment arm only)
b) Documented AF/AT/AFL on ambulatory monitoring/12-lead ECG after the 90 day post-ablation blanking period (treatment arm)/AAD optimization period (control arm).
    - Minimum of 30 seconds on ambulatory monitoring or 10 seconds on 12-lead ECG.
    - Note: Documented occurrence and treatment of typical right-sided cavotricuspid isthmus dependent atrial flutter is not considered a failure if confirmed by entrainment maneuvers during EP testing.
c) Any subsequent AF surgery or ablation in the left atrium.
d) Any subsequent cardioversion after the 90 day post-ablation blanking period (treatment arm)/AAD optimization period (control arm).
e) Class I or III antiarrhythmic drug (or sotalol) use after the 90 day blanking period (treatment arm only).

The AAD optimization period is defined as the first 90 days after AAD initiation (control arm). The post-ablation blanking period is defined as the first 90 days after the index ablation procedure (treatment arm). Recurrences of atrial arrhythmias during the AAD optimization/blanking periods will not be counted in the determination of the first clinical failure for the primary endpoint.

Within the AAD optimization period/post-ablation blanking period, recurrent arrhythmias can be managed with medications or cardioversions. Reablation will be considered a primary endpoint failure at all times, including during the 90 day post-ablation blanking period.

Acute procedural failure (treatment arm only) is defined as:

a) Inability to isolate all accessible targeted pulmonary veins (assessed for entrance block and, where assessable, exit block) during the index ablation procedure.
b) Left atrial non-PVI ablations including but not limited to, ablation of linear lesions
c) Use of a non-study device in the left atrium.

5.1.4.2. Primary Safety Endpoint

The following adverse events will be counted towards the primary safety endpoint:

- TIA within 7 days
- Cerebrovascular accident within 7 days
- Major bleeding that requires transfusion or results in a 20% or greater fall in hematocrit (HCT) within 7 days
- Development of a significant pericardial effusion within 30 days. A significant pericardial effusion is one that results in hemodynamic compromise, requires elective or urgent pericardiocentesis, or results in a 1-cm or more pericardial effusion as documented by echocardiography.
- Symptomatic PV stenosis within 12 months; accompanied by one of the following: 50%-70% reduction in diameter of the pulmonary vein, with symptoms not explained by other conditions; OR >70% reduction in diameter of the pulmonary vein
- MI within 7 days
- PNI unresolved at 12 months
- Atrial-esophageal fistula within 12 months
- Major vascular complication that requires intervention, prolongs the hospital stay, or requires hospital admission (within 7 days).

5.1.5. Secondary Endpoints

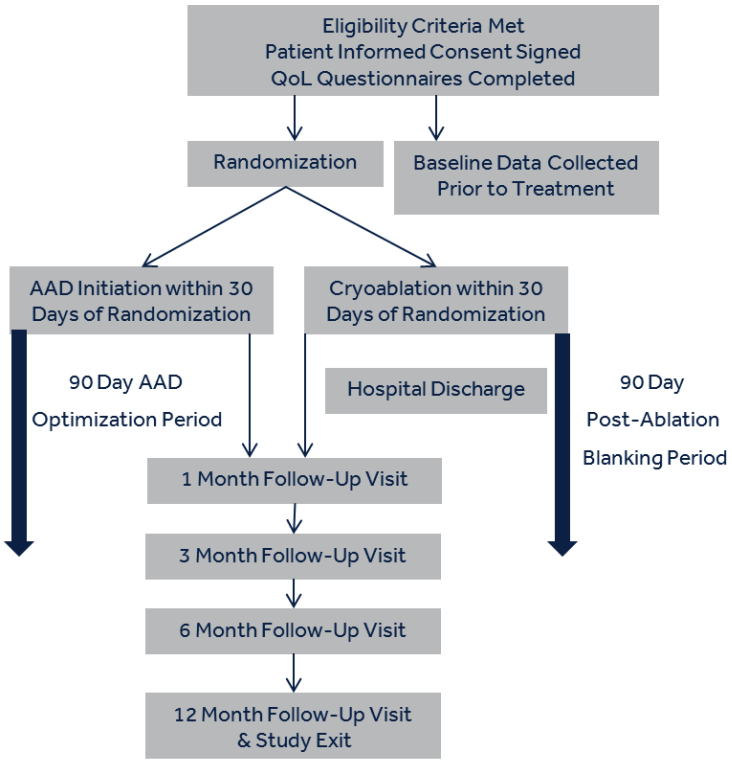
1. The difference in composite scores from the AFEQT questionnaire taken at baseline and 12 month visits, and the difference in composite scores for the EQ-5D questionnaire taken at baseline and 12-month visits.
   - The AFEQT and EQ-5D questionnaires will be utilized for this objective. The AFEQT questionnaire is an atrial fibrillation specific health-related quality of life questionnaire to assess the impact of AF on a subject's life. The overall score ranges from 0–100, where 0 corresponds to complete disability and 100 correspond to no disability. The EQ-5D questionnaire is a standardized instrument for measuring generic health status. The EQ-5D has two sections. The first section is a descriptive section where the subject checks a box by the most appropriate statement. The second section is a visual analog scale.
2. 12-month rates of cardiovascular health care utilization (HCU) events, and 12-month rates of cardioversion (either electrical or pharmacological).
   - The number of cardiovascular-related hospitalizations, emergency department visits, and unscheduled visits will be reported and compared between the treatment and control arms.
   - The number of electrical and pharmacological cardioversions experienced by subjects will be reported and compared between the treatment and control arms.

5.1.6. [redacted]

6. Study Design

Medtronic, Inc. is sponsoring the STOP AF First study; a prospective, interventional, multi-center, randomized, controlled, unblinded clinical study. The study will be conducted at up to 30 sites in the US and up to 10 in Europe. Two hundred and ten (210) subjects will be enrolled. The maximum number of subjects that may be randomized at a single center will be 31 subjects (15% of the total subjects randomized). No greater than 50% of the subjects will be enrolled outside of the US. There is no minimum number of required enrollments per site; however, sites will be encouraged to enroll and randomize at least 5 subjects. Subjects will be randomized to either AAD therapy (control arm) or cryoablation (treatment arm). Subjects will be followed at 1 month, 3 months, 6 months, and 12 months following either cryoablation or AAD initiation. Subjects will be exited from the study at the 12 month follow-up visit. At least one Arctic Front Advance CryoAblation Catheter will be used per subject in the treatment arm. Additional catheters may be used in the case of reablation or crossover ablation (at least one per subject).

Figure 1: Study Design



6.1. Duration

All randomized study subjects will be followed from the time of consent through 12 months post-index cryoballoon ablation procedure (treatment arm), or AAD initiation (control arm).

Subjects will be exited from the study at the conclusion of the 12 month follow-up visit. The expected total study duration is approximately 30 months, representing 18 months of enrollment and 12 months of subject follow-up. Subjects will not be replaced with newly enrolled subjects upon early study exit. The objectives will be analyzed for a Premarket Approval Supplement (PMA-S) after all randomized subjects complete 12 months of follow-up after the index cryoballoon ablation procedure (treatment arm), or AAD initiation (control arm).

6.2. Rationale

The study has primary objectives designed to evaluate the safety and effectiveness of the Arctic Front Advance™ Cardiac CryoAblation Catheter for treatment of recurrent symptomatic paroxysmal AF. In the US, there are no ablation catheters approved to treat patients with paroxysmal AF unless they have demonstrated intolerance or refractoriness to anti-arrhythmic drug therapy. The study will provide patients with more options for treatment and the possibility of improving their health and quality of life and a decrease in stroke risk. If successful, the STOP AF First study will demonstrate meaningful therapeutic benefit in this population. This evaluation will support an indication expansion for the treatment of recurrent symptomatic paroxysmal AF. The study will be considered successful if it meets the primary objectives, contingent upon FDA review and approval.

The study will compare cryoablation to AAD therapy, the current standard of care for subjects experiencing atrial fibrillation for the first time.

Cryoablation efficacy will be demonstrated by showing that subjects in the cryoablation arm will experience a higher rate of efficacy success than the AAD arm (treatment success described in Section 5.1.4.1). The STOP AF Pivotal trial showed an efficacy success rate of 69.9%. Several trials were completed comparing radiofrequency ablation to AADs in the same non-drug refractory patient population (Nielsen, et al. 2012) (Morillo, et al. 2014) (Wazni, et al. 2005). The RAAFT-2 study monitored for recurrent arrhythmia in a manner similar to the requirements of this protocol; they required regular and symptomatic transtelephonic monitor transmissions (Morillo, et al. 2014). In RAAFT-2, approximately 45% of subjects in the AAD arm experienced recurrent atrial fibrillation by one year. The superiority analysis in this study is designed to show that subjects in the cryoablation treatment arm will experience less AF recurrence than subjects in the AAD arm, assuming similar recurrence rates to those in the STOP AF Pivotal trial and RAAFT-2.

Cryoablation safety will be demonstrated by showing that the rate of a pre-specified list of known potential complications is consistent with previous trials and current literature (Packer, et al. 2013).

6.3. Minimization of Bias

Selection of subjects, treatment of subjects, and evaluation of study data are potential sources of bias. Methods incorporated in the study design to minimize potential bias include (but are not limited to):

- Subjects will undergo screening to confirm eligibility for enrollment with defined inclusion/exclusion criteria prior to enrollment.
- Subject demographics will be collected at baseline in order to later assess possible characteristics that may influence endpoints.
- All centers and geographies will use the same version of the clinical investigation plan and case report forms.
- All investigational center personnel and Medtronic personnel will be trained on their respective aspects of the study using standardized training materials.
- All investigational center personnel will be trained on and required to follow the CIP.
- An independent Clinical Events Committee (CEC) will be utilized regularly to review and adjudicate reported adverse events and deaths.
- An independent core lab will be utilized to review and adjudicate all ECG recordings from study required 12-lead ECGs and ambulatory monitoring.
- A statistical analysis plan (SAP) will be developed prior to analyzing data. The plan will document all pre-specified analyses and analysis methods.
- Monitoring will be conducted to review adherence to the CIP and perform source data verification per the Monitoring Plan.
- A maximum of 31 treated subjects will be allowed at a single investigational center to ensure an even distribution of total subjects across centers.
- All study investigators in all geographies will be required to comply with 21CFR Part 54, Financial Disclosure by Clinical Investigators.

In summary, potential sources of bias that may be encountered in this clinical study have been considered and minimized by thorough, careful study design.

7. Product Description

7.1. General

All cryoablation devices, the console, and accessories used in this study are market released in the US and Europe. Investigational centers will utilize the commercially released Arctic Front Advance™ Cardiac CryoAblation Catheters (and future commercially released generations). There are no changes to the Arctic Front Advance™ Cardiac CryoAblation Catheters anticipated or planned at this time. Any changes made to these devices during this investigation will be subject to IDE Modification Reporting Requirements, as applicable. Any changes to devices that require an update to the CIP will be addressed in a CIP amendment. Changes may not result in a CIP amendment.

Instructions for use for all devices used in this study are provided in their respective manuals. Labeling language requirements will be consistent with local regulations. Maintenance and calibration of equipment will be performed in accordance with each center's standard processes. Device information is provided in Table 4 and described below.

Table 4: Device Information

Component	Model Number(s)	Geography	Manufacturer
Arctic Front Advance™ CryoAblation Catheter	2AF234	US (investigational)	Medtronic CryoCath LP
	2AF284		
	2AF233	Europe (non-investigational, CE marked and used within approved indication)	Medtronic CryoCath LP
	2AF283		
Freezor® *MAX* Cardiac CryoAblation Catheter	239F3	US (non-investigational)	Medtronic CryoCath LP
	239F5		
	209F3	Europe (non-investigational, CE marked and used within approved indication)	
	209F5		
FlexCath Advance™ Steerable Sheath	4FC12	US (non-investigational) Europe (non-investigational, CE marked and used within approved indication)	Medtronic CryoCath LP
Achieve™ Mapping	990063-015	US (non-investigational)	Medtronic, Inc.

Component	Model Number(s)	Geography	Manufacturer
Catheter	990063-020	Europe (non-investigational, CE marked and used within approved indication)	
Achieve Advance Mapping Catheters	2ACH25	US (non-investigational) Europe (non-investigational, CE marked and used within approved indication)	Medtronic, Inc.
	2ACH20		
	2ACH15		
CryoCath CryoAblation Console	104A2/Model 10000-003	US (non-investigational)	Medtronic CryoCath LP
	106A3/Model 10000-008-004		
	106A3/Model 10000-008-08		
	106E2/Model 10000-008-002	Europe (non-investigational, CE marked and used within approved indication)	Medtronic CryoCath LP
	106E2/Model 10000-008-06		
Coaxial Umbilical Cable	203CX	US (non-investigational) Europe (non-investigational, CE marked and used within approved indication)	Medtronic CryoCath LP
	203CXC		
Electrical Umbilical Cable	2035U	US (non-investigational) Europe (non-investigational, CE marked and used within approved indication)	Medtronic CryoCath LP
	2035UC		
Manual Retraction Kit	20MRK	US (non-investigational) Europe (non-investigational, CE marked and used within approved indication)	Medtronic CryoCath LP

7.2. Arctic Front Advance™ Cardiac CryoAblation Catheters

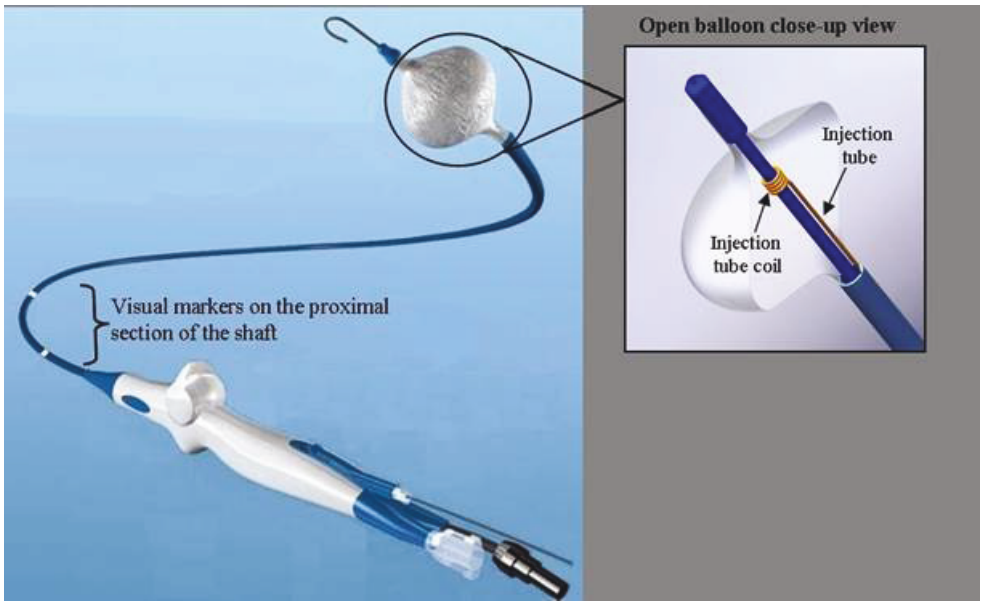
In the US, the Arctic Front Advance™ Cardiac CryoAblation Catheters (23mm and 28mm) are FDA approved and indicated for the treatment of drug refractory recurrent symptomatic paroxysmal atrial fibrillation.

The investigational indication in the US is for the treatment of recurrent symptomatic paroxysmal atrial fibrillation without the requirement that the AF be drug refractory.

In Europe, the Arctic Front Advance™ Cardiac CryoAblation Catheters (23mm and 28mm) are CE marked and indicated for the treatment of patients with atrial fibrillation. The catheter is not considered investigational for the intended patient population in Europe, as it is being used within the approved indication.

The catheters are sterile, single use, minimally invasive intravascular balloon catheters specifically designed for tissue cryoablation. The Arctic Front Advance™ Cardiac CryoAblation Catheter is used together with the CryoConsole and related devices. Arctic Front Advance™ Cardiac CryoAblation Catheters are percutaneously advanced to the heart chamber from the femoral access via a transseptal sheath in the vasculature. Once the catheter reaches the left atrium, the balloon is inflated and the cooling segment creates circumferential lesions at the antrum of the targeted pulmonary veins.

Figure 2: Arctic Front Advance™ Cardiac Cryoablation Catheter



7.3. Freezor ® *MAX* Cardiac CryoAblation Catheters

In the US and Europe, the Freezor® *MAX* Cardiac CryoAblation Catheter is market released and approved for use in the study intended patient population, therefore, is not considered investigational.

Approved indication in the US: The Freezor® *MAX* Cardiac CryoAblation Catheter is used as an adjunctive device in the endocardial treatment of paroxysmal atrial fibrillation in conjunction with the Arctic Front Advance™ Cardiac CryoAblation Catheter.

Approved indication in Europe: The Freezor® *MAX* Cardiac CryoAblation Catheter is intended for use in the treatment of cardiac arrhythmias.

The Freezor® *MAX* Cardiac CryoAblation Catheter is a flexible, steerable catheter used to ablate cardiac tissue. It is used together with the CryoConsole and related components. The tip of the Freezor® *MAX* Cryocatheter reaches cryoablation temperatures when refrigerant is injected from the CryoConsole to the tip of the catheter. The catheter tip has an integrated thermocouple for temperature reading capability. The catheter is introduced into the vasculature by traditional minimally invasive techniques.

7.4. FlexCath Advance™ Steerable Sheath

The FlexCath Advance™ Steerable Sheath is a percutaneous introducer fitted with a hemostasis valve to allow for introduction, withdrawal and swapping of catheters and wires while providing a barrier preventing air ingress into the valve and minimizing blood loss. A side-port with stopcock is integrated into the hemostasis valve to allow continuous drip infusion, injection through the center lumen, flushing, aspiration, blood sampling and pressure monitoring. The FlexCath Advance™ Steerable Sheath is intended to allow sheath deflection to facilitate catheter positioning. It is supplied sterile and packaged together with a dilator.

Figure 3: FlexCath Advance™ Steerable Sheath with Cryoablation Catheter

7.5. Achieve™ or Achieve Advance™ Mapping Catheter

The Achieve™ and Achieve Advance™ Mapping Catheters are intra-cardiac electrophysiology diagnostic catheters indicated for multiple electrode electrophysiological mapping of the cardiac structures of the heart, i.e., recording or stimulation only. The Achieve™ and Achieve Advance Mapping Catheters are designed to obtain electrograms in the atrial regions of the heart.

Figure 4: Achieve™ Mapping Catheter

7.6. CryoCath CryoAblation Console

The CryoConsole houses the electronics and compatible software for controlling and recording the ablation procedure, stores and controls delivery of liquid refrigerant under high pressure through the co-axial umbilical to the catheter, recovers the expanded refrigerant vapor from the catheter under vacuum, and disposes of the refrigerant through the hospital scavenging system.

The hardware controls the safety monitoring system while the software provides the user interface patient information, procedure temperature, time set point in automatic mode and procedure data information. The most current market approved software version available will be used at the site.

Figure 5: CryoCath CryoAblation Console

7.7. Coaxial Umbilical Cable

The Sterile Coaxial Umbilical delivers the Nitrous Oxide (N2O) gas from the console to the catheter and transports refrigerant vapors from the catheter to the console, which is then vented into the hospital scavenging system.

Figure 6: Coaxial Umbilical Cable

7.8. Electrical Umbilical Cable

The Sterile Electrical Umbilical is an electrical extension cable that transports:

- Temperature feedback from the catheter to the console
- Leak detection signals from the catheter to the console
- Blood sensor signals from the catheter to the console
- Pressure sensor form the catheter to the console

Figure 7: Electrical Umbilical Cable

7.9. Manual Retraction Kit

The manual retraction kit contains one large syringe, one 3-way stopcock and a coaxial-to-luer adaptor. The kit is used during the rewrap procedure of the Arctic Front Advance™ Cardiac CryoAblation Catheter if the physician cannot retract the catheter using the normal catheter retraction cycle.

Figure 8: Manual Retraction Kit

7.10. Additional Study Devices

Medtronic may incorporate additional components, software, and devices into this clinical study as they receive appropriate license or regulatory approval and are released commercially by Medtronic in the region where they will be used providing that the scientific soundness of the study is not adversely affected as evaluated by Medtronic.

7.11. Product Training Requirements

Physicians performing the cryoablation procedure must have been trained in the handling of Arctic Front Advance™ Cardiac CryoAblation Catheter and CryoCath Cardiac CryoAblation System. They must be qualified by Medtronic AF Solutions Training and Education (US ONLY), and must have performed at least 20 ablation procedures with Arctic Front or Arctic Front Advance™ and associated products.

7.12. Packaging

In the US and Europe, the Arctic Front Advance™ Cardiac CryoAblation Catheters will not be labeled as investigational. These devices will be considered investigational upon opening per the CIP (US only). Commercially available products will be used for the study.

7.13. Investigational Device Storage, Handling and Traceability

The Arctic Front Advance™ Cardiac CryoAblation Catheters used in this study are commercially available in the US and Europe; they will not be labeled as investigational and will not be provided to the investigational centers.

The Arctic Front Advance™ Cardiac CryoAblation Catheter will be considered investigational in the US when opened with the intent to use in this study. The catheter is market-released and will be used within the approved indication in Europe, therefore, will be considered non-investigational in Europe.

In the US, device tracking information will be entered into the study database for any catheter that is considered investigational in this study. The device tracking information must be maintained and updated when the investigational catheter is disposed of or returned to Medtronic.

NOTE: this is a deviation to Section 9.8 of the ISO standard because device accountability for the Arctic Front Advance™ Cardiac CryoAblation Catheters will not be performed in Europe and only upon package opening with the intent of using the catheter for a study subject in the US.

8. Investigator/Investigator Center Selection

All clinical Investigators managing the subject's arrhythmia must be qualified practitioners and experienced in the diagnosis and treatment of subjects with atrial arrhythmias. Investigators performing the cryoablation procedure must have been trained in the handling of Arctic Front Advance™ Cardiac CryoAblation Catheters.

The role of the Principal Investigator is to implement and manage the day-to-day conduct of the clinical investigation as well as ensure data integrity and the rights, safety and well-being of the subjects involved in the clinical investigation.

The minimum required criteria for a Principal Investigator and proposed investigational center are listed below:

- Investigator/site is qualified by training, education, and relevant experience appropriate to the use of the product and associated procedures.
- Investigator/site expects to have adequate time and resources to conduct the study throughout the duration of the study.
- Investigator/site has access to an adequate number of eligible subjects.
- Ability to comply with applicable Institutional Review Board (IRB)/Ethics Committee (EC) and regulatory requirements.
- Investigator is not debarred, disqualified, or working under sanctions in applicable regions.

Center personnel training will be completed prior to participation in this clinical study.

9. Center Activation

During the activation process (prior to subject enrollment), Medtronic will train center personnel on the CIP, relevant standards and regulations, informed consent, and on data collection and reporting tools. If new members join the study center team, they will receive training on the applicable clinical study requirements relevant to their role before contributing to the clinical study.

Prior to performing study related activities, all local regulatory requirements shall be fulfilled, including, but not limited to the following:

- IRB/MEC approval (and membership roster/voting list) of the current version of the CIP, Patient Informed Consent Form, subject facing materials, Report of Prior Investigation, Investigator Brochure as required by local laws and other materials, as necessary.
- Regulatory authority approval or notification (as required per local law)
- Fully executed Clinical Trial Agreement (CTA) and Investigator Statement where applicable
- Financial Disclosure of Investigators
- Curriculum Vitae (CV) of Investigators and key members of the investigation center team (as required by local law) (in Europe, CVs are required for the Principal Investigator and all center members who have been delegated tasks)
- Documentation of delegated tasks
- Documentation of study training

Documentation of delegated tasks must be completed prior to any person other than the Principal Investigator performing study activities.

Additional requirements imposed by the IRB/MEC and regulatory authority shall be followed.

In addition, all participating center staff must be trained on the current version of the CIP and must be delegated by the Principal Investigator to perform study related activities.

Medtronic will provide each study center with documentation of study center/Investigator readiness in the form of a center readiness letter; this letter must be received prior to subject enrollment. Additional center personnel included after the initial activation will be notified when all requirements have been completed.

10. Selection of Subjects

10.1. Study Population

The study population includes adult patients with recurrent symptomatic paroxysmal atrial fibrillation. The AF classifications that will be used for this study are defined in the 2017 HRS/EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation. (Calkins, et al. 2017)

Paroxysmal AF is defined as AF that terminates spontaneously or with intervention within 7 days of onset.

Patients in persistent AF are excluded from the study. Persistent AF is defined as continuous AF that is sustained beyond 7 days.

10.2. Subject Enrollment

Patients will be screened to ensure they meet all of the inclusion criteria and none of the exclusion criteria prior to study enrollment. Institutional Review Board (IRB)/Ethics Committee (EC) and Medtronic approval of this CIP and the Informed Consent Form (ICF) must be obtained prior to enrolling subjects in the study. Subjects are considered enrolled in the study upon signing and dating the ICF. Subjects must provide informed consent (IC) before any study related procedures occur.

10.3. Inclusion Criteria

- A diagnosis of symptomatic paroxysmal AF with the following documentation: (1) physician's note indicating recurrent self- terminating AF or paroxysmal AF; and (2) any ECG documented AF within 6 months prior to enrollment.
- Age 18-80

10.4. Exclusion Criteria

- History of AF treatment with class I or III antiarrhythmic drug, including sotalol, with the intention to prevent an AF recurrence. However, patients pretreated with above AAD for less than 7 days with the intention to convert an AF episode are allowed.
- Prior persistent AF (continuous AF that is sustained >7 days)
- Left atrial diameter greater than 5.0 cm
- Prior left atrial ablation or left atrial surgical procedure
- Presence or likely implant of a permanent pacemaker, biventricular pacemaker, loop recorder, or any type of implantable cardiac defibrillator (with or without biventricular pacing function)
- Presence of any pulmonary vein stents
- Known presence of any pre-existing pulmonary vein stenosis
- Pre-existing hemidiaphragmatic paralysis
- Presence of any cardiac valve prosthesis
- Moderate or severe mitral valve regurgitation or stenosis
- Any cardiac surgery, myocardial infarction, PCI / PTCA or coronary artery stenting which occurred during the 90 day interval preceding the date the subject signed the Informed Consent Form
- Unstable angina
- NYHA class III or IV congestive heart failure and/or known left ventricular ejection fraction (LVEF) less than 45%

- Diagnosis of primary pulmonary hypertension
- Rheumatic heart disease
- Thrombocytosis, thrombocytopenia
- Contraindication to anticoagulation therapy
- Active systemic infection
- Hypertrophic cardiomyopathy
- Cryoglobulinemia
- Known reversible causes of AF, including but not limited to uncontrolled hyperthyroidism, severe obstructive sleep apnea, and acute alcohol toxicity.
- Any cerebral ischemic event (strokes or TIAs) which occurred during the 180 day interval preceding the date the subject signed the Informed Consent Form, or any known unresolved complications from previous stroke/TIA
- Existing thrombus
- Pregnancy
- Patient with life expectancy that makes it unlikely 12 months of follow-up will be completed.
- Current or anticipated participation in any other clinical trial of a drug, device or biologic during the duration of this study not pre-approved by Medtronic
- Patients with contraindications to a Holter monitor
- Unwilling or unable to comply fully with study procedures and follow-up

11. Study Procedures

Prior to performing study related procedures, all sites must have IRB/EC approval as well as documentation from Medtronic of center readiness.

11.1. Schedule of Events

The visit schedule and data collection requirements are summarized in Table 5.

Table 5: Visit Schedule and Data Collection Requirements Summary

	Baseline	Procedure	Hospital Discharge	1M	3M	6 & 12 M	Unscheduled	Reablation/ Crossover Ablation
		Treatment Arm Only						
Informed Consent	X							
Randomization	X							
Inclusion/Exclusion	X							
Medical History	X							
Physical Exam	X							
Pregnancy Screening[1]	X							
Review Medications	X		X	X	X	X	X	X
Review of AF Symptoms	X			X	X	X	X	X
Collect Health Care Utilization Information				X	X	X	X	X
12 Lead ECG	X		X	X	X	X	X	
EQ-5D & AFEQT	X					X		X
Trans-thoracic Echocardiogram (TTE)[2]	X							
Trans-esophageal Echocardiogram (TEE)[3]		X						X

[1] Required only for female subjects of childbearing potential.
[2] Only required if data not available from within prior 6 months from consent date.
[3] TEE must be performed in all subjects who present to the ablation procedure in atrial fibrillation lasting more than 48 hours in duration (or of an unknown duration). However, the TEE is not required if the subject has adequate systemic anticoagulation that has been maintained for at least 3 weeks prior to presenting to the ablation procedure in AF. TEE must be performed if subjects have a CHA2DS2-VASc ≥2 and present to the procedure with a sub-therapeutic INR (<2.0) or if the subject has had a significant interruption of NOACs. A significant interruption of NOACs is defined as any missed dose within 21 days prior to the ablation procedure.

	Baseline	Procedure	Hospital Discharge	1M	3M	6 & 12 M	Unscheduled	Reablation/ Crossover Ablation
		Treatment Arm Only						
Ablation Procedure Data		X						X
24 hour continuous ambulatory ECG monitoring						X		
Patient Activated Ambulatory ECG Monitoring[4]					X			
Adverse Events	X	X	X	X	X	X	X	X
Device Deficiencies	As they occur							
Study Deviations	As they occur							
Chest X-ray (treatment arm only)	If phrenic nerve injury is detected during the procedure, the subject will be evaluated with inspiration/expiration chest x-ray at PHD and all follow-up visits until resolved.							
MRI or CT Scan (treatment arm only)	Required only for subjects with suspected PV stenosis.							

11.1.1. Modes of Data Collection

Multiple modes of data collection may be employed to support the collection of required visit data. This includes such methods as:

- In-office patient clinic visit
- Direct to patient contact (i.e. telephone, email, mail contact, etc.)
- Remote technology transmissions/uploads

11.2. Medications

Information regarding drugs prescribed to treat atrial arrhythmias will be collected, including the purpose for their use/reason for modification, and start and stop dates. Information regarding anticoagulation mediations will be collected, including start and stop dates.

Control Arm (AAD): Subjects must initiate a Class I or III AAD within 30 days of randomization. It is recommended that AADs be initiated as soon as possible after randomization, with a target of within 14 days. The investigator should choose the appropriate AAD per his or her standard of care; however, amiodarone should only be used if other AADs were not tolerated or failed. The 2014 AHA/ACC/HRS

[4] Subjects shall submit ECG transmissions weekly and whenever symptoms occur after the AAD optimization/post-ablation blanking periods through 12 month follow-up.

Guideline for the Management of Patients with AF should be consulted for AAD prescriptions. Modifications to AADs (type or dosage increase) may be made for up to 90 days after AAD initiation. This is referred to as the AAD optimization period. Dosing of AADs can be individually tailored until the end of the AAD optimization period. After the optimization period, further AAD therapy optimization or change should be avoided or at least allowed only up to physicians' discretion to guarantee the safety of the patients. The possible concomitant use of beta blockers can still be optimized after the optimization period.

Treatment Arm (Cryoablation): Subjects may be prescribed Class I or III AADs for up to 80 days post-ablation procedure at the discretion of the Investigator. Subjects must stop taking all Class I or III AADs before day 81 post-ablation. Use of amiodarone is not permitted.

Anticoagulation requirements for all subjects:

Anticoagulation pre-procedure should be determined based upon the subjects CHA_2DS_2-VASc score.

a. Oral anticoagulants are required if the subject has had a prior stroke or TIA, or if the subject has a CHA_2DS_2-VASc score ≥2. When anticoagulation is required, subjects must take it for at least 21 days prior to an ablation procedure.
b. Oral anticoagulants are not required for subjects with nonvalvular AF and a CHA_2DS_2-VASc score of 0 or 1.

Note: TEE must be performed within one day prior to the cryoablation procedure if subjects have a CHA_2DS_2- VASc ≥2 and present to the procedure with a sub-therapeutic INR (<2.0) or if the subject has had a significant interruption of NOACs. A significant interruption of NOACs is defined as any missed dose within 21 days prior to the ablation procedure.

11.3. Subject Consent

Patient informed consent (IC) is defined as a legally effective documented confirmation of a subject's (or their legally authorized representative, US ONLY) voluntary agreement to participate in a particular clinical study after information has been given to the subject on all aspects of the clinical study that are relevant to the subject's decision to participate. This process includes obtaining an Informed Consent Form (ICF) and an Authorization to Use and Disclose Personal Health Information that has been approved by the study center's IRB/EC and signed and dated by the subject (or their legally authorized representative, US ONLY). A subject may only consent after information has been given to the subject on all aspects of the clinical investigation that are relevant to the subject's decision to participate. Informed consent may be given by their legally authorized representative (US ONLY) only if a subject is unable to make the decision to participate in a clinical investigation. In such cases, the subject shall also be informed about the clinical investigation within his/her ability to understand.

Prior to enrolling subjects, the ICF must have been approved by each center's IRB/EC. Each site must also use an Authorization to Use and Disclose Personal Health Information/Research Authorization/other privacy language as required by law. The ICF must be controlled (i.e. versioned and dated) to ensure it is clear which version(s) were approved by the IRB/EC. Any modifications to the sample ICF must be reviewed and approved by Medtronic and the IRB/EC reviewing the application prior to enrolling subjects.

The Investigator must notify the subject (US ONLY: or their legally-authorized representative) of any significant new findings about the study that become available during the course of the study which are pertinent to the safety and well-being of the subject. This could impact a subject's willingness to

participate in the study. If relevant, approval may be requested from subjects to confirm their continued participation.

Prior to initiation of any study-specific procedures, documented IC must be obtained from the subject (or their legally authorized representative, US ONLY). Likewise, privacy or health information protection regulation may require subjects to sign additional forms to authorize centers to submit subject information to the study sponsor. The IC process must be conducted by the principal Investigator or an authorized designee, and the ICF and the Authorization to Use and Disclose Personal Health Information/Research Authorization/other privacy language as required by law must be given to the subject (or their legally authorized representative, US ONLY) in a language he/she is able to read and understand. The process of IC must be conducted without using coercion, undue or improper influence on, or inducement of the subject to participate by the Investigator or other center personnel. The informed consent process shall not waive or appear to waive the subject's legal rights. The language used shall be as non-technical as possible and must be understandable to the subject and the impartial witness, where applicable.

The subject must have ample time and opportunity to read and understand the ICF to inquire about details of the study, and to decide whether or not to participate in the clinical study. All questions about the study should be answered to the satisfaction of the subject. When the subject decides to participate in the clinical study, the ICF and the Authorization to Use and Disclose Personal Health Information/Research Authorization/other privacy language as required by law must be signed and personally dated by the subject (or their legally authorized representative, except in Europe) and either the Investigator or the Investigator's authorized designee, as required by local law. If applicable, witness shall also sign and personally date the consent form to attest that the information in the ICF was accurately explained and clearly understood by the subject, and that IC was freely given.

In Europe, include a personally dated signature by the Principal Investigator or authorized designee responsible for conducting the informed consent process. The Principal Investigator or designee must conduct the informed consent discussion.

A copy of the ICF and the Authorization to Use and Disclose Personal Health Information/Research Authorization/other privacy language as required by law, signed and dated as required by law, must be provided to the subject.

If consent is obtained the same day the subject begins participating in study-related procedures, it must be documented in the subject's case history that consent was obtained prior to participation in any study related procedures. It is best practice for the IC process to be documented in the subject's case history, regardless of circumstance. In the event the subject cannot read and/or write, a witnessed (impartial third party) ICF will be allowed, provided detailed documentation of the process is recorded in the subject's case history and the witness signs and dates the ICF to attest that the information was accurately explained and that informed consent was freely given. In Europe, when a subject cannot read and/or write, an independent witness shall be present throughout the process, the written ICF and any other information shall be read aloud and explained to the prospective subject. The subject should "make his mark" (sign or otherwise physically mark the document so as to indicate consent) on the ICF as well. The ICF should document the method used for communication with the prospective subject and the specific means by which the prospective subject communicated agreement to participate in the study.

The original of the signed ICF and the Authorization to Use and Disclose Personal Health Information/Research Authorization/other privacy language as required by law must be filed in the hospital/clinical chart and/or with the subject's study documents. The ICF and the Authorization to Use and Disclose Personal Health Information/Research Authorization/other privacy language as required by law should also be available for monitoring and auditing. Any Medtronic Field personnel who support the study procedure must be able to review the subject's signed and dated ICF and verify its completeness prior to proceeding with the procedure. In the event the Medtronic Field personnel identify an ICF as being incomplete, the study procedure will not be allowed to occur until the consent of the subject can be adequately and appropriately obtained.

11.4. Randomization and Treatment Assignment

Enrolled subjects are eligible for randomization after all inclusion and none of the exclusion criteria are met and after the baseline QoL questionnaires are completed. Subjects will be randomized in a 1:1 fashion to undergo a cryoablation procedure (treatment arm) or receive AAD therapy (control arm).

See Section 11.5.2 for control arm procedures and Section 11.5.3 for treatment arm procedures.

Subjects will be randomized using an electronic randomization system. The randomization schedule will be stratified by study site to ensure that within each study site randomization is approximately 1:1.

Subjects will be analyzed according to a modified intention-to-treat protocol: subjects who withdraw their informed consent prior to the index cryoablation procedure or initiation of AAD therapy will be excluded from the analysis of the primary safety and efficacy endpoints. Otherwise, the standard intention-to-treat protocol is applied: subjects who receive either therapy, regardless of what it actually is, will be analyzed according to their randomization status. This allows for the protection of the benefits of randomization, while avoiding the problem of attrition and adverse events occurring in the time between randomization and the initiation of treatment, which, due to the practicality of scheduling can be up to 30 days. All randomized subjects should be encouraged to comply with the study procedures until study closure.

11.5. Description of All Study Procedures and Visits

11.5.1. Enrollment & Baseline

The patient is considered a subject enrolled in the study upon completion of the IC process. The date the subject signed the ICF and HIPAA/data protection authorization/or other privacy language where required by law must be documented in the subject's medical records.

All baseline assessments must be performed prior to treatment (cryoablation procedure or initiation of AADs). The following evaluations will be performed after the subject signs the ICF, unless previously performed as part of routine clinical evaluations within the specified windows:

<u>Within 6 months prior to the date the subject signed the Informed Consent Form:</u>

- Trans-thoracic echocardiogram (TTE) for the collection of left atrial size, left ventricular ejection fraction, and mitral valve impairment. A repeat TTE procedure for the purpose of this study is not required if a TTE was performed within 6 months of the date the subject signed the Informed Consent Form and all data are available.

Within 30 days prior to the date the subject signed the Informed Consent Form:

- Physical examination
- CHA2DS2-VASc Score
- 12 lead ECG
- Demographics
- Medical history

After the date the subject signed the Informed Consent Form, but prior to cryoablation procedure or AAD treatment:

Note: The time between randomization and the procedure/AAD initiation must not exceed 30 days. It is recommended that AAD initiation occur within 14 days of randomization. It is recommended that the cryoablation procedure occur within 21 days of randomization.

- Assessment of all factors specified for evaluation under Inclusion Criteria and Exclusion Criteria (Section 10.3 and 10.4), including TTE (required prior to randomization).
- EQ-5D and AFEQT Questionnaires (required prior to randomization)
- Randomization
- Pregnancy screen (required only for female subjects of childbearing potential)
- For this study, a woman of childbearing potential is defined as a premenopausal female capable of becoming pregnant (not sterilized or post-menopausal).
- Review of AF symptoms
- Review of medications to treat atrial arrhythmias and anticoagulation medications
- Transesophageal Echocardiogram (TEE) (treatment arm only)
- TEE must be performed in all subjects who present to the ablation procedure in atrial fibrillation lasting more than 48 hours in duration (or of an unknown duration). However, the TEE is not required if the subject has adequate systemic anticoagulation that has been maintained for at least 3 weeks prior to presenting to the ablation procedure in AF.
- TEE must be performed if subjects have a CHA2DS2- VASc ≥2 and present to the procedure with a sub-therapeutic INR (<2.0) or if the subject has had a significant interruption of NOACs. A significant interruption of NOACs is defined as any missed dose within 21 days prior to the ablation procedure.
- Performance of a TEE in subjects who are in sinus rhythm at the time of ablation or eligible subjects that have been in AF for 48 hours or less prior to AF ablation may be considered but is not mandatory.
- The subject will not proceed with the study ablation procedure and will be exited from the study if a cardiac thrombus is visualized.
- TEE, when required, must be performed within 1 day of the ablation procedure (on the day of or within the day prior to).

11.5.2. Control Arm- AAD Initiation

Subjects must initiate a Class I or III AAD within 30 days of randomization. It is recommended that AADs be initiated as soon as possible after randomization, with a target of within 14 days. The investigator should choose the appropriate AAD per his or her standard of care; however, amiodarone should only be used if other AADs were not tolerated or failed. The 2014 AHA/ACC/HRS Guideline for the Management of Patients with AF should be consulted for AAD prescriptions. Modifications to AADs (type or dosage increase) may be made for up to 90 days after AAD initiation. This is referred to as the AAD optimization

period. Dosing of AADs can be individually tailored until the end of the AAD optimization period. After the optimization period, further AAD therapy optimization or change should be avoided or at least allowed only up to physicians' discretion to guarantee the safety of the patients. The possible concomitant use of beta blockers can still be optimized after the optimization period. Reason for AAD modification must be documented.

Crossovers from AAD therapy to cryoablation will be allowed only if the subject in the control group is deemed a treatment failure. Crossovers must be pre-approved by the Medtronic Clinical Study Manager. Approval will be granted after verification that the subject is an efficacy failure.

Treatment failure is defined in section 5.1.4.1.

11.5.3. Treatment Arm- Cryoablation Procedure

Within 30 days of randomization, perform the pulmonary vein isolation procedure using the Arctic Front Advance™ Cardiac CryoAblation Catheter.

If needed, a Freezor® *MAX* Cardiac CryoAblation Catheter may also be utilized for gap ablation to complete electrical isolation of the pulmonary veins and creation of ablation lines between the inferior vena cava and the tricuspid valve. The Investigator is to perform the procedure according to the procedural steps in this CIP and the Instructions for Use for the catheters. Appropriate sedation and venous access should be attained at the Investigator's standard practice according to their institution's pre-established procedures/guidelines at the time of the procedure.

The use of any non-study device in the left atrium is not permitted.

Only the Medtronic FlexCath sheath family should be used with the Arctic Front Advance™ Cardiac CryoAblation Catheter. The use of other sheaths may damage the device. The Investigator may choose compatible guidewires and mapping catheters at his or her discretion.

11.5.3.1. Esophageal Visualization and Temperature Monitoring

Ensure an esophageal temperature monitor is used for each cryoablation application. The cryoapplication must be ceased if the temperature reaches ≤ 15°C.

11.5.3.2. Pre-procedure Anticoagulation

Current recommendations for anticoagulation are found in the 2017 HRS/EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation (Calkins, et. al. 2017). Anticoagulation pre-procedure should be determined based upon the subjects CHA_2DS_2-VASc score. Oral anticoagulants are required if the subject has had a prior stroke or TIA, or if the subject has a CHA_2DS_2-VASc score ≥2. When anticoagulation is required, subjects must take it for at least 21 days prior to an ablation procedure. Oral anticoagulants are not required for subjects with nonvalvular AF and a CHA_2DS_2-VASc score of 0 or 1.

11.5.3.3. Intra-procedure Anticoagulation

Heparin should be administered prior to or immediately following transseptal puncture during AF ablation procedures and adjusted to achieve and maintain an ACT of 300-400 during the procedure, with ACT recommended to be checked at 30 minutes intervals. Administration of protamine following ablation to reverse heparin should be considered.

11.5.3.4. Post-procedure Anticoagulation

Systemic oral anticoagulation should be initiated on the day of the procedure and is recommended for at least two months following an AF ablation procedure. Decisions regarding the continuation of systemic anticoagulation agents more than two months following ablation should be based on the patient's risk factors for stroke as estimated by the CHA_2DS_2-VASc score and not on the presence or type of AF.

Discontinuation of systemic anticoagulation therapy post ablation is not recommended in patients who are at high risk of stroke as estimated by the CHA_2DS_2-VASc score.

11.5.3.5. Diaphragm Movement

a. Prior to the first cryoablation application, the Investigator will make a fluoroscopic recording of inspiratory and expiratory movement of the diaphragm.

b. Continuous phrenic nerve pacing with abdominal palpitation must be performed for all right pulmonary vein cryoapplications and should be considered for all cryoapplications. Additional methods of phrenic nerve monitoring are encouraged, such as diaphragmatic compound motor action potential (CMAP).

c. After the last cryoablation application, the Investigator will make a fluoroscopic recording of inspiratory and expiratory movement of the diaphragm.

11.5.3.6. Balloon Pulmonary Vein (PV) Cryoablation

a. Every effort consistent with subject welfare will be made to treat all PVs or their anomalous equivalents.

b. The catheter will be advanced into the left atrium over the mapping catheter or guidewire and inflated. Once inflated, the catheter will be tracked over the Achieve™ catheter and positioned at the entrance of the PV.

c. Assess the positioning, contact and occlusion of the PV by the catheter's balloon by injection of contrast material, ultrasound imaging, or other technique. Reposition as needed.

d. Each pulmonary vein must be assessed for entrance block and, where assessable, exit block to demonstrate electrical isolation.

e. It is recommended that the Investigator use cryoapplications of three (3) minutes each. Once PV isolation has been achieved, one (1) additional application of three (3) minutes at the same PV should be performed; however, it is up to the operator's discretion to assess application time and necessity of the additional freeze given factors such as time to isolation of prior application(s), temperature of prior application(s), risk of collateral damage, etc.

f. Upon the Investigator's assessment of procedure completion, isoproterenol and/or adenosine may be used to assess pulmonary vein isolation.

11.5.3.7. Other Ablations During Index Procedure

a. Ablation of the cavotricuspid isthmus is required in subjects with a history of typical atrial flutter or inducible cavotricuspid isthmus depend atrial flutter. Complete an assessment for bi-directional block if this procedure is performed. Any commercially released catheter deemed appropriate for the procedure may be used.

b. The following are not allowed:

- Left atrial non-PVI ablations including but not limited to, ablation of linear lesions, complex fractionated electrograms or non-PV triggers
- Ablation using any non-study device in the left atrium

11.5.3.8. Cardioversion

a. Electrical or pharmacological cardioversion to sinus rhythm must be attempted following the PVI portion of the procedure if sinus rhythm wasn't restored. Cardioversion may be performed prior to PVI if needed.

11.5.3.9. Procedure Documentation

During the procedure the investigator will document the following:

- Catheters used (i.e. Arctic Front Advance™, Freezor® MAX and Achieve™ Mapping Catheter, etc.)
- Minimum temperature for each cryoapplication
- Duration of each cryoapplication
- Vein location for each cryoapplication (e.g. right superior PV)
- Use of phrenic nerve pacing or other phrenic nerve monitoring technique for each cryoapplication, specifically those cryoapplications surrounding the RS and RI PVs
- Demonstrated electrical block and, if real-time signals are available, time to isolation
- Adjunctive catheters, mapping or visualization devices, sedation type, procedure information, esophageal temperature, ACT, cardioversion use and fluoroscopy time will be collected.

11.5.4. Hospital Discharge

At or shortly before hospital discharge, the following will be performed and collected:

- Adverse event assessment
- In the case of suspected PV stenosis, Magnetic Resonance Imaging (MRI) or Computerized Tomography Scanning (CT scan) is required.
- Review medications
- 12 lead ECG
- Chest X-ray: For any subject whose post-procedural fluoroscopy demonstrated study-related PNI, a follow-up chest X-ray, including inspiration and expiration films, will be performed
- Review study requirements with the subject to help ensure compliance with follow-up procedures
- Evaluate the subject's neurological status per institutional standard of care to determine if a formal neurological consultation should be performed for stroke assessment. Report any adverse events that result from the neurologic evaluation and consultation, if applicable.

11.5.5. Medication Compliance

Information regarding medications prescribed for anticoagulation or to treat atrial arrhythmias will be collected through study exit. The following information will be collected for medications to treat atrial arrhythmias: medication name, purpose for use, start and stop dates, dose, dosage changes (and reasons for changes), and route of administration. Data collection for anticoagulation medication will be limited to medication name and start and stop dates.

Control Arm (AAD):

Subjects must initiate a Class I or III AAD within 30 days of randomization. It is recommended that AADs be initiated as soon as possible after randomization, with a target of within 14 days. The investigator should choose the appropriate AAD per his or her standard of care; however, amiodarone should only be used if other AADs were not tolerated or failed. The 2014 AHA/ACC/HRS Guideline for the Management of Patients with AF should be consulted for AAD prescriptions. Modifications to AADs (type or dosage increase) may be made for up to 90 days after AAD initiation. This is referred to as the AAD optimization period. Dosing of AADs can be individually tailored until the end of the AAD optimization period. After the optimization period, further AAD therapy optimization or change should be avoided or at least allowed only up to physicians' discretion to guarantee the safety of the patients. The possible concomitant use of beta blockers can still be optimized after the optimization period.

Cryoablation (Treatment Arm):

Per physician discretion, class I or III antiarrhythmic, including sotalol, medication use is permitted for up to 80 days following the ablation procedure. Use of amiodarone is not permitted. Prescriptions for these drugs must not allow a quantity that will last longer than 80 days post-procedure. It is recommended that site personnel contact subjects on day 80 post-ablation procedure to ensure they have stopped taking class I or III antiarrhythmic drugs. Class I or III antiarrhythmic drug use after the 90 day blanking period will be considered a primary endpoint failure.

Systemic oral anticoagulation should be initiated on the day of the procedure and is recommended for at least two months following an AF ablation procedure. Decisions regarding the continuation of systemic anticoagulation agents more than two months following ablation should be based on the patient's risk factors for stroke as estimated by the CHA_2DS_2-VASc score and not on the presence or type of AF.

Discontinuation of systemic anticoagulation therapy post ablation is not recommended in patients who are at high risk of stroke as estimated by the CHA_2DS_2-VASc score.

All Subjects:

All other medications (those that are not specified above) are permitted in the study, with the exception of investigational drugs that may confound the study results. Beta-blockers may be prescribed per standard of care.

11.5.6. Subsequent Ablation Procedures

Any subsequent ablation in the left atrium or AF surgery will be counted as an endpoint failure. There is no 90 day blanking period for repeat ablation. Subsequent ablations and AF surgeries will be documented on an eCRF.

Subsequent ablations in the right atrium are allowed (e.g. typical atrial flutter ablation).

11.5.7. Cardioversions

Electrically and pharmacologically cardioverting the subject to sinus rhythm is allowed in the 90 day post-procedure blanking period (treatment arm)/AAD optimization period (control arm) at the discretion of the Investigator. Electrically or pharmacologically cardioverting the subject to sinus rhythm after the blanking period/AAD optimization period will be counted as an efficacy endpoint failure.

11.5.8. Scheduled Follow-up Visits

After the index cryoablation procedure (treatment arm) or AAD initiation (control arm) is reported in the study database, the database will calculate the target dates and windows for each visit to the site. Should a subject miss a visit or the visit fall outside the pre-specified window, a study deviation must be reported and the original follow-up schedule maintained for subsequent visits.

Data analyses include follow-up visits, regardless of whether the visit occurs within the window. Therefore, a late visit is preferred over a missed visit but must be accompanied by a deviation. Follow-up visit windows are listed in Table 6 and are based on days post-index procedure or AAD initiation.

Table 6: Follow-up Visit Windows

Occurrence/ Visit	Window (Calculated days post-procedure or AAD initiation)	
	Window Start	Window End
Randomization	-30 days	Day 0
Index Cryoablation Procedure/ AAD initiation	Day 0	Day 0
1 month office	31 days	51 days
3 month office	91 days	111 days
6 month office	165 days	195 days
12 month office	365 days	395 days

The following activities will occur at the follow-up visits:

11.5.8.1. One Month Office Visit

- Review medications
- Adverse event assessment
- Review symptoms suggestive of recurrent AF/AT/AFL
- Health care utilization assessment- collect information about hospitalizations or emergency department visits experienced by the subject since the last visit
- 12 lead ECG
- Chest X-ray
    - For any subject whose post-procedural fluoroscopy demonstrated study-related PNI, a follow-up chest X-ray, including inspiration and expiration films, will be performed if the PNI was unresolved at hospital discharge.
- In the case of suspected PV stenosis, Magnetic Resonance Imaging (MRI) or Computerized Tomography Scanning (CT scan) is required. It is not required at this visit if it was already completed at an earlier visit and PV stenosis was confirmed.

11.5.8.2. Three Month Office Visit

- Review medications
- Adverse event assessment
- Review symptoms suggestive of recurrent AF/AT/AFL
- Health care utilization assessment- collect information about hospitalizations or emergency department visits experienced by the subject since the last visit
- 12 lead ECG
- Provide the subject with patient-activated ambulatory monitoring equipment; provide instructions for and weekly and symptomatic transmissions.
- Chest X-ray
    - For any subject whose post-procedural fluoroscopy demonstrated study-related PNI, a follow-up chest X-ray, including inspiration and expiration films, will be performed if the PNI was unresolved at the one month visit
- In the case of suspected PV stenosis, Magnetic Resonance Imaging (MRI) or Computerized Tomography Scanning (CT scan) is required. It is not required at this visit if it was already completed at an earlier visit and PV stenosis was confirmed.

11.5.8.3. Six Month Office Visit

- Review medications
- Adverse event assessment
- Review symptoms suggestive of recurrent AF/AT/AFL
- Health care utilization assessment- collect information about hospitalizations or emergency department visits experienced by the subject since the last visit
- 12 lead ECG
- 24h continuous ECG monitoring with ambulatory monitoring equipment
- EQ-5D and AFEQT Questionnaires
- Review the patient-activated ambulatory monitoring instructions with the subject.
- Chest X-ray, including inspiration and expiration films, is required for subjects whose PNI was unresolved at the 3 month visit
- In the case of suspected PV stenosis, Magnetic Resonance Imaging (MRI) or Computerized Tomography Scanning (CT scan) is required. It is not required at this visit if it was already completed at an earlier visit and PV stenosis was confirmed.

11.5.8.4. Twelve month Office Visit

- Review medications
- Adverse event assessment
- Review symptoms suggestive of recurrent AF/AT/AFL
- Health care utilization assessment- collect information about hospitalizations or emergency department visits experienced by the subject since the last visit
- 12 lead ECG
- 24h continuous ECG monitoring with ambulatory monitoring equipment. The subject will be instructed to apply the continuous monitoring patches and complete the 24 hours of continuous monitoring within 7 days prior to the 12 month visit. It is recommended that the study personnel call the subject to remind them of this requirement. If the subject is not able to apply the device prior to the visit, it may be applied by study personnel at the 12 month visit.
- EQ-5D and AFEQT Questionnaires
- Collect the ambulatory monitoring equipment and return to Medtronic (or designee). If the subject did not perform the continuous monitoring prior to the 12 month visit, apply the device to the subject to complete 24 hour continuous monitoring. Give the subject instructions on how to return the equipment.
- Chest X-ray, including inspiration and expiration films, is required for subjects whose PNI was unresolved at the 6 month visit
- In the case of suspected PV stenosis, Magnetic Resonance Imaging (MRI) or Computerized Tomography Scanning (CT scan) is required. It is not required at this visit if it was already completed at an earlier visit and PV stenosis was confirmed.
- Inform the subject they have completed the study

11.5.9. Unscheduled Office Visits

An unscheduled visit is defined as any unplanned cardiovascular-related office visit at the study site that is performed by personnel participating in the study and occurs between CIP required visits. Submit to the core lab any 12 lead ECG or continuous monitoring completed in conjunction with an unscheduled office visit. The following information is required to be collected at unscheduled follow-up visits:

- Review medications
- Adverse event assessment
- Review symptoms suggestive of recurrent AF/AT/AFL
- Health care utilization assessment- collect information about hospitalizations or emergency department visits experienced by the subject since the last visit
- 12 lead ECG

11.5.10. Re-Ablation/Crossover Ablation

- Obtain approval from Medtronic for crossover ablations (not required for treatment arm reablation)
- Perform the following assessments prior to the cryoablation:
    - Review medications
    - Adverse event assessment
    - Review symptoms suggestive of recurrent AF/AT/AFL
    - EQ-5D and AFEQT Questionnaires
    - Health care utilization assessment- collect information about hospitalizations or emergency department visits experienced by the subject since the last visit
- Procedure Data:
    - Catheters used (i.e. Arctic Front Advance™, Freezor® MAX and Achieve™ Mapping Catheter, etc.)
    - Minimum temperature for each cryoapplication
    - Duration of each cryoapplication
    - Vein location for each cryoapplication (e.g. right superior PV)
    - Use of phrenic nerve pacing or other phrenic nerve monitoring technique for each cryoapplication, specifically those cryoapplications surrounding the RS and RI PVs
    - Demonstrated electrical block and, if real-time signals are available, time to isolation
    - Adjunctive catheters, mapping or visualization devices, sedation type, procedure information, esophageal temperature, ACT, cardioversion use and fluoroscopy time will be collected
    - Pulmonary vein isolation stats from previous ablation (re-ablations only)

11.5.11. 12 lead Electrocardiograms

All study required 12 lead ECGs will be sent to the core lab. The core lab will be responsible for adjudication of atrial arrhythmias for the primary objective of the study. The core lab will send the results of all ECG analyses to the Investigators for appropriate follow-up, if necessary, and assessment for adverse event reporting. Copies of additional source documents may be requested.

11.5.12. Ambulatory Monitoring

Market- released ambulatory monitoring equipment will be distributed by a core lab to centers after activation has occurred. Subjects will be provided with a small patient-activated electronic ambulatory

monitoring device after the AAD optimization (control arm) or post-ablation blanking period (treatment arm) ends. This device will serve two functions:

- 24 hour continuous monitoring: This is traditionally done using a Holter monitor. The investigative site personnel will apply the device patches for the subject during the subject's 6 month visit and train the subject how to apply the device. The subject will be asked to apply the continuous monitoring patches themselves prior to the 12 month study visit. Additionally, subjects may be asked to perform 24 hour continuous monitoring on their own if they miss a scheduled study visit.
- Patient-activated mode: Subjects will be asked to transmit ECG data weekly and whenever they experience AF symptoms. This mode does not require adhesive patches; the subject simply holds the device to his or her chest for a short period of time.

In both modes, the data automatically transmits to the core lab via a secured cell phone connection.

The core lab will manage maintenance, calibration and tracking of the ambulatory monitoring equipment. The core lab will be responsible for adjudication of rhythm documentation for the primary efficacy objective of the study. The core lab will send the results of all ambulatory monitoring analyses to the Investigators for appropriate follow-up, if necessary, and assessment for adverse event reporting.

Subjects will return the ambulatory monitoring equipment at the 12 month follow-up visit.

11.5.13. Study Exit

Subjects will be exited from the study upon completion of the 12 month follow-up visit. For information about subject withdrawal and discontinuation, see section 11.10.

11.6. Assessment of Efficacy

The primary efficacy objective is based on the data collected as discussed in section 5.1.1 and 5.1.4.

11.7. Assessment of Safety

The secondary safety objective is based on the Adverse Event data collected. Further information on the collection and assessment of safety data is discussed in section 13.

11.8. Recording Data

The study will collect data using an electronic data management system for clinical studies. Centers will enter data onto eCRFs within the database. The core lab will also enter data onto CRFs within a separate electronic database.

Procedures in the CIP require source documentation. Source documentation will be maintained at the study center. Source documents, which may include worksheets, subject medical records, and console files, must be created and maintained by the investigational center team. The data reported on the eCRFs shall be derived from source documents and be consistent with these source documents, and any discrepancies shall be explained in writing. The eCRF may be considered source for the following data collection elements:

- Time of isolation of the cryoablation catheter
- Esophageal temperature
- Investigator assessment of adverse event or death relatedness and severity

- Date center became aware of the adverse event, device deficiency or death
- Reason for study deviation
- Database generated patient reference ID

When copies or print-outs of the source documents are made, center personnel must sign and date any copies or printouts of original source documents with a statement that this is complete and true reproduction of the original source document. The sponsor or a regulatory authority may audit or inspect the study center to evaluate the conduct of the study.

The clinical Investigator(s)/institution(s) shall allow study related monitoring, audits, IRB/EC review and regulatory inspection by providing direct access to source data/documents. Further detail on data management is provided in Section 17.3.

11.9. Deviation Handling

A study deviation is defined as an event within the study that did not occur according to requirements specific to the CIP or CTA. Every attempt must be made to avoid study deviations. Prior approval by Medtronic is expected in situations where the Investigator anticipates, contemplates, or makes a conscious decision to deviate. In countries following ISO 14155:2011, prior approval for study deviations will be reported to local authorities and ethics boards per local requirements. If the deviation affects subject's rights, safety and well-being, or the scientific integrity of the study, prior approval from ethics board and/or competent authority (CA) is also required, depending on local legislations. Prior approval is not required when a deviation is necessary to protect the safety, rights, or well-being of a subject in an emergency or in unforeseen situations beyond the Investigator's control (e.g. subject failure to attend scheduled follow-up visits, inadvertent loss of date due to computer malfunction, inability to perform required procedures due to subject illness). Subjects' failure to submit ambulatory monitoring transmissions per the CIP do not require a deviation to be reported. Ambulatory monitoring transmission compliance will be tracked by Medtronic personnel and the Core Lab.

For medically justifiable conditions which preempt a subject's ability to complete a study required procedure, it may be permitted to report only one deviation which will apply to all visits going forward. This may also apply for other unforeseen situations (e.g. the subject permanently refuses to complete a study required procedure and the data will not contribute to the primary endpoint analysis.). However, prior approval from Medtronic is required for such situations.

All study deviations must be reported to Medtronic regardless of whether they are medically justifiable, pre-approved by Medtronic, an inadvertent occurrence, or taken to protect the subject in an emergency. The description of the deviation and justification must be documented and submitted to Medtronic via eCRF completion.

In the event the deviation involves a failure to obtain a signed Informed Consent Form, or is made to protect the life or physical well-being of a subject in an emergency, the deviation must be reported to the IRB/EC as well as Medtronic within five (5) working days. Reporting of all other study deviations should comply with IRB/EC policies and/or local laws and must be reported to Medtronic as soon as possible upon the site becoming aware of the deviation. Refer to

Table 9 for reporting requirements.

Medtronic is responsible for reviewing deviations, assessing their significance, and identifying any necessary corrective and/or preventive actions (e.g. amend the CIP, conduct additional training, and terminate the investigation). Repetitive or serious Investigator compliance issues may result in initiation

of a corrective action plan with the Investigator and center, and in some cases, may necessitate suspending a center's ability to enroll until the problem is resolved, or ultimately terminating the Investigator's participation in the study. Medtronic will provide center-specific reports to Investigators summarizing information on deviations that occurred at the investigational center on a periodic basis.

11.10. Subject Withdrawal or Discontinuation

A subject can withdraw from the study at any time. If the subject wishes to exit from the study (i.e. the subject revokes consent), the center is required to document the reason for exit on an eCRF. In addition, centers shall follow the regulations set forth by their IRB/EC.

Prior to exiting a subject from the study, it is recommended to follow the subject until all ongoing device and/or procedure related adverse events are resolved or unresolved with no further actions planned. An unscheduled office visit should be attempted if the subject exits the study outside of a scheduled follow-up visit.

Following exit, subjects will continue to receive standard medical care. Upon exiting from the study, no further study data will be collected or study visits will occur for the subject. All data available through the time of the subject's exit will be used for analysis.

Reasons for subject withdrawal or discontinuation include:

- Subject is lost to follow-up
- Subject did not meet inclusion/exclusion criteria after the date the subject signed the Informed Consent Form and prior to randomization.
- The subject was randomized to the treatment arm, but no cryoballoon ablation procedure was attempted
- The subject was randomized to the control arm, but no AAD was initiated
- Subject chooses to withdraw (e.g., Informed Consent Form withdrawal, relocation to another geographic location)
- Investigator deems withdrawal necessary (e.g., medically justified, inclusion/exclusion criteria not met, failure of subject to maintain adequate study compliance)
- The sponsor or regulatory authority decides the study will be closed or a particular center will be closed

The following information is required to be collected at early study exit:

- Reason for exit must be documented on the eCRF and in the subject's medical record
- An unscheduled office visit should be attempted if the subject exits the study outside of a scheduled follow-up visit

In the case that the subject is determined to be lost to follow-up, details of a minimum of two attempts and the method of attempt (e.g., one letter and one phone record or two letters) to contact the subject must be recorded. In addition, follow the regulations set forth by the governing IRB/EC.

12. Risks and Benefits

12.1. Potential Risks

Medtronic follows rigorous Quality Assurance and Control procedures throughout the life of a product, from the business analysis phase through development, market release, and post-market surveillance. The residual risks associated with the Arctic Front Advance™ Cardiac CryoAblation Catheter have been found to be acceptable and have been mitigated to the fullest extent possible. The potential benefits related to the use of the Arctic Front Advance™ Cardiac CryoAblation Catheter have been determined to outweigh any potential risks. The device has never been recalled.

There are potential risks and side effects associated with Class I and III AADs. A complete list of known risks associated with the drugs used in this study can be found within their approved labeling.

There are potential risks and side effects associated with ablation procedures. The Investigator shall describe risks in further detail when asked by the subject. The risks must be continuously monitored, assessed and documented by the Investigator. Possible additional risks for participating the study include the following (although others are possible) and are further defined in Appendix F.

- Anemia-deficiency of red blood cells or of hemoglobin in the blood resulting in weariness.
- Anxiety-a feeling of worry, nervousness, or unease.
- Back pain- pain felt in the lower or upper back.
- Bleeding e.g. bleeding into the retroperitoneal space.
- Bronchitis, cough, pneumonia-inflammation of the lungs can be caused by a virus or bacteria.
- Cardiac tamponade-pressure on the heart as a result of fluid collecting in the sac surrounding the heart.
- Cardiopulmonary arrest-cessation of blood circulation and/or respiration due to dysfunction of the heart and/or lungs.
- Chest discomfort/pain/pressure-includes a range of feeling from sharp stabbing to dull ache in the chest.
- Cold feeling-having a low or inadequate temperature.
- Complications associated with contrast agents-adverse effects of contrast agents used during the procedure (e.g. allergic reaction or radio contrast nephropathy).
- Complications associated with medications commonly utilized during the procedure-known risks of medications commonly used during the procedure (e.g. narcotics, anxiolytics, other pain medications, anti-vasospasm agents).
- Complications at catheter insertion site in the groin:
    - AV fistula-an abnormal connection between an artery and a vein (i.e., cause by needle insertion through the femoral artery and vein).
    - Hematoma/Bruising-a collection of blood in the tissue surrounding the catheter insertion site.
    - Infection-localized redness, heat swelling and pain at the catheter insertion site.

  - Pain-discomfort at the catheter insertion site that can range from mild to severe.
  - Pseudoaneurysm-a collection of blood in the tissue surrounding the catheter insertion site due to ongoing leaking of blood from a blood vessel.
  - Significant bleeding-blood loss from the catheter insertion site requiring surgery or transfusion of 2 or more units of packed red blood cells (PRBCs).
- Coronary artery spasm, vasospasm-constriction of a blood vessel.
- Death-a complication or deterioration of health ultimately leading to a patient's death.
- Dissection of a blood vessel-a tear within the wall of a blood vessel.
- Dizziness, lightheadedness-feeling faint, woozy, weak or unsteady.
- Embolism-formation and dislodgement of a blood clot (thrombus) or dislodgement of cholesterol/plaque within the blood vessel, which travels downstream into small vessels, blocking blood flow and causing temporary or permanent damage to organs distal to blockage. Emboli are known to cause myocardial infarction, transient ischemic attack, stroke/cardiovascular accident, blurred vision, visual changes, paralysis, paresis, or kidney damage, peripheral ischemia and may ultimately lead to incapacitation or death. Symptomatic and non-symptomatic.
- Endocarditis –inflammation of the inner surface of the heart.
- Esophageal injury –damage to your swallowing tube, atrio-esophageal fistula - abnormal passageway between the heart and esophagus, hematemesis (vomiting blood).
- Fatigue- extreme tiredness.
- Fever- abnormally high body temperature.
- Gastroparesis- delayed gastric emptying.
- Headache- pain in the head.
- Heartblock requiring permanent pacemaker implantation
- Heart rhythm disturbances-disruption of normal heart rate or rhythm (e.g. atrial flutter, tachycardia, bradycardia).
- Hemothorax –collection of blood around the lungs.
- Hiccups- involuntary spasm of the diaphragm and respiratory organs.
- Hypertension-high blood pressure.
- Hypotension-low blood pressure.
- Infection (e.g. sepsis)
- Injury to lung- (e.g. bronchial lesion, hemoptysis, constriction, pulmonary hemorrhage, bronchia fistula).
- Mild skin discomfort or irritation-redness sensitivity of the skin cause during or after the procedures (e.g. electrodes used with the ECG and Holter recorder might cause mild skin discomfort or irritation or some skin discomfort following electrode removal or tape removal).
- Nausea-a sensation of unease and discomfort in the upper stomach with an urge to vomit.

- Perforation of a blood vessel or cardiac tissue-unintended puncture through the wall of a blood vessel or cardiac tissue.
- Pericardial effusion- fluid collecting in the sac that surrounds the heart.
- Pericarditis –inflammation of the sac that surrounds the heart.
- Phrenic nerve injury –damage to the nerve that controls breathing.
- Pleural effusion –collection of extra fluid around the lungs.
- Pneumothorax – collapsed lung.Pulmonary edema- excess fluid in the lungs.
- Pulmonary hypertension- high blood pressure that affects the arteries in the lungs and the right side of the heart.Pulmonary vein hematoma- trauma to the pulmonary vein.
- Pulmonary vein stenosis –blockage in the blood vessels takes blood from the lungs to the heart.
- Renal dysfunction-kidneys fail to adequately filter waste products from the blood.
- Right sided heart failure- right side of the heart is not pumping blood to the lung normally.
- Shivering- body shaking.
- Shortness of breath- difficulty breathing.
- Small ischemic cerebral (brain) lesions not accompanied by clinically apparent symptoms have been found on brain imaging performed after an AF ablation procedure. So far, the relationship between these lesions and an increased incidence of stroke or transient ischemic attack (a mini stroke) has not been established. However, whether these lesions will result in long term cognitive decline (e.g. loss of memory and trouble thinking) is unclear.
- ST elevation- the ST segment of an ECG is abnormally high above the baseline.
- Sore throat- pain in the throat.
- Urinary infection- an infection in the urinary system.
- Vascular complications requiring surgery-damage to an artery (e.g. femoral) or vein requiring surgical repair.
- Vasovagal reaction- reflex of the involuntary nervous system that causes the heart to slow down and blood pressure drops.
- Vomiting-forceful expulsion of stomach contents through the mouth and/or nose.

The risks of participating in this clinical study are the same as the cryoablation procedure risks, and also include:

- Risks/discomforts associated with sedation/anesthesia:
    - Hoarseness.
    - Myalgia (pain in the muscles).
    - Numbness and tingling of the fingers.
    - Diarrhea.
    - Dry mouth.
    - Sleepiness.

- Radiation exposure due to potential for additional CT/MRI scan or Chest X-rays.
- Patches and adhesive used with the ambulatory monitoring equipment may cause skin discomfort or irritation, or some skin discomfort following patch removal.

12.2. Risk Minimization

Medtronic has attempted to minimize the potential risks to subjects in this study by taking the following actions:

- Selecting qualified investigators and training study personnel on the CIP.
- Requiring that investigators be actively involved in the procedure and follow-up of the subjects who undergo a study procedure.
- Providing guidelines for subject selection and evaluation.
- Requiring that subjects be followed at regular intervals following the ablation procedure to monitor for recurrence of atrial arrhythmias and to assess for adverse events.

12.3. Potential Benefits

The Arctic Front Advance™ Cardiac CryoAblation Catheter may reduce or eliminate atrial fibrillation in subjects who have not yet failed an AAD; however, some subjects may not receive this benefit. Subjects in the control arm treated with an AAD may also reduce or eliminate atrial fibrillation; however, some subjects may not receive this benefit. The information gained from the study could result in improved management of atrial fibrillation. It is possible that subjects will experience no benefit from participating in the study.

12.4. Risk-Benefit Rationale

The cohort of subjects for inclusion in the study is symptomatic as a result of their atrial fibrillation, but has not yet tried AAD therapy. Cryoablation therapy offers the opportunity to reduce the episodes of atrial fibrillation without the subject having to take AADs or experience the side effects of AAD therapy. There is no incremental risk or benefit for subjects in the control arm in the study.

In the US, there are no ablation catheters approved to treat subjects with paroxysmal atrial fibrillation who have not yet attempted AAD therapy. If successful, this study could demonstrate meaningful therapeutic benefit in this patient population and provide patients with additional treatment options earlier in disease progression.

13. Adverse Event Assessments

Timely, accurate, and complete reporting and analysis of safety information for clinical studies are crucial for the protection of subjects. Reporting and analysis of safety data are mandated by regulatory authorities worldwide. Medtronic has established procedures in conformity with worldwide regulatory requirements to ensure appropriate reporting of safety information. This study is conducted in accordance with these procedures and regulations.

Since the safety reporting requirements and classification systems vary for each regulatory agency, requirements from all geographies are taken into account for the collection and reporting of safety information.

Where the definition indicates "device", it refers to any device used in the study. This might be the device under investigation or any market released component of the system. Adverse events (AE) will be classified according to the definitions below.

13.1. Definitions/Classifications

General	
Adverse Event (AE)	Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users, or other persons, whether or not related to the investigational device NOTE 1 This definition includes events related to the investigational medical device or comparator NOTE 2 This definition includes events related to the procedures involved NOTE 3 For users or other persons, this definition is restricted to events related to investigational medical devices. (ISO 14155:2011, 3.2)
Adverse Device Effect (ADE)	Adverse Device Effect (ADE): adverse event related to the use of an investigational medical device. Note 1: This definition includes any adverse event resulting from insufficient or inadequate instructions for use or the deployment, implantation, installation, or operation, or any malfunction of the medical device. Note 2: This definition includes any event resulting from user error or from intentional misuse of the medical device (ISO 14155:2011, 3.1)

Device Deficiency (DD)	Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. NOTE: Device deficiencies include malfunctions, use errors and inadequate labeling (ISO 14155:2011, 3.15)
Seriousness	
Serious Adverse Event (SAE)	Adverse event that a) led to death, b) led to serious deterioration in the health of the subject, that either resulted in 1) a life-threatening illness or injury, or 2) a permanent impairment of a body structure or a body function, or 3) in-patient or prolonged hospitalization (>24 hours), or 4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function, c) led to fetal distress, fetal death or a congenital abnormality or birth defect NOTE 1: Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event. (ISO 14155:2011, 3.37)
Serious Adverse Device Effect (SADE)	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event. (ISO 14155:2011, 3.36)
Unanticipated Adverse Device Effect (UADE)	Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, an (investigational) device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the CIP or applicable (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects. (21 CFR 812.3(s))
Unanticipated Serious Adverse Device Effect (USADE)	Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report. NOTE: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report. (ISO 14155:2011 3.42)

Relatedness	
Procedure related	An adverse event directly related to any portion of the procedure that encompasses cryoablation.
Cryoablation system related	An adverse event that results from the presence or performance (intended or otherwise) of the cryoablation system (including the Arctic Front Advance, Freezor MAX, FlexCath Sheath, Achieve Mapping Catheter, CryoConsole, Manual Retraction Kit)
Cardiovascular related	An adverse event relating to the heart and the blood vessels or the circulation.
AAD related	An adverse event for which there is a reasonable possibility that the drug caused the adverse event.
Relatedness Definitions	
Not Related	Relationship to the device or procedures can be excluded when: • The event is not a known side effect of the product category the device belongs to or of similar devices and procedures; • The event has no temporal relationship with the use of the device or the procedures; • The serious event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible; • The discontinuation of medical device application or the reduction of the level of activation/exposure – when clinically feasible – and reintroduction of its use (or increase of the level of activation/exposure) do not impact the serious event; • The event involves a body-site or an organ not expected to be affected by the device or procedure; • The serious event can be attributed to another cause (e.g., an underlying or concurrent illness/clinical condition, an effect of another device, drug, treatment, or other risk factors); • The event does not depend on a false result given by the device used for diagnosis (when applicable); • Harms to the subject are not clearly due to use error; • In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the event.
Possibly Related	The relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases were relatedness cannot be assessed or no information has been obtained should also be classified as possible.
Causal Relationship	The event is associated with the device or study procedures beyond reasonable

<table>
<tr><td></td><td>doubt when:
The event is a known side effect of the product category the device belongs to or of similar devices and procedures;
The event has a temporal relationship with device use/application or procedures;
The event involves a body-site or organ that the device or procedures are applied to or the device or procedures have an effect on;
The serious event follows a known response pattern to the medical device (if the response pattern is previously known);
The discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure) impact on the serious event (when clinically feasible);
Other possible causes (e.g., an underlying or concurrent illness/clinical condition or/and an effect of another device, drug, or treatment) have been adequately ruled out;
Harm to the subject is due to error in use;
The event depends on a false result given by the device used for diagnosis (when applicable);
In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.</td></tr>
<tr><td colspan="2">Other</td></tr>
<tr><td>Unavoidable AEs</td><td>An adverse event inherent to a surgical procedure that is expected to occur in all subjects for a projected duration according to the investigator's opinion, including, but not limited to the list provided below.

These are not reportable AEs unless they occur after or last longer than the timeframe specified. If any other events below are classified as serious they must be reported as an adverse event.

Unavoidable AEs<table><tr><th>Event Description</th><th>Time (Hours) from the Surgical Procedure</th></tr><tr><td>Anesthesia related nausea/vomiting</td><td>24</td></tr><tr><td>Low-grade fever (<100°F or < 37.8°C)</td><td>48</td></tr><tr><td>Mild to moderate bruising / ecchymosis in groin area/ groin pain</td><td>168</td></tr><tr><td>Sleep problems (insomnia)</td><td>72</td></tr><tr><td>Back pain related to lying on the table</td><td>72</td></tr></table></td></tr>
</table>

13.2. Reporting of Adverse Events

For the purposes of this study, the following Adverse Events will be collected starting at the time the subject signs the Informed Consent Form through the duration of the subject's participation in the study:

- All procedure related AEs
- All cryoablation system related AEs
- All AAD related AEs
- All cardiovascular related AEs
- All Serious Adverse Events (SAEs), regardless of relatedness

Reporting of these events to Medtronic will occur on an Adverse Event (AE) Form, including a description of AE, date of onset of AE, date of awareness of site, treatment, resolution, assessment of both the seriousness and the relatedness to the investigational device.

Each AE must be recorded on a separate AE Form. Exceptions include:

- Documented pre-existing conditions are not considered AEs unless the nature or severity of the condition has worsened. Additionally, arrhythmia episodes that are not new or worsening conditions and for which no action is taken are not reportable as AEs.
- Unavoidable Adverse Events, listed in section 13.1 need not be reported unless the adverse event worsens or is present outside the stated timeframe post-procedure.
- Cardioversions (DC or Drug) for recurrent symptomatic atrial fibrillation and other atrial arrhythmias are not considered serious adverse events.

For any changes in status of a previously reported adverse event (i.e. change in actions taken, change in outcome, change in relatedness), an update to the original AE must be provided. All adverse events must be followed until the adverse event has been resolved, is unresolved with no further actions planned, the subject exits the study or until study closure, whichever occurs first.

In the event that a subject is exited from the study prior to study closure, all efforts should be made to continue following the subject until all unresolved procedure or cryoablation system related adverse events, as classified by the investigator, are resolved or they are unresolved with no further actions planned.

At the time of study exit, all adverse events with an outcome of "Unresolved, further actions or treatment planned" must be reviewed and an update to the original AE must be reported. At a minimum, if there are no changes to the description, relatedness, test and procedures or actions taken, the outcome must be updated to reflect "Unresolved at time of study closure."

Subject deaths are also required to be reported. Refer to section 13.3.1 for Subject Death collection and reporting requirements.

13.2.1. Device Deficiencies

Device deficiency (DD) information will be collected throughout the study and reported to Medtronic. Note that device deficiencies that result in an adverse device effect (ADE) to the subject should be captured as an Adverse Event only.

Device deficiencies that did not lead to an AE but could have led to a Serious Adverse Device Effect (SADE) (i.e., if suitable action had not been taken, if intervention had not been made, or if the circumstances had been less fortunate) require immediate reporting. For AEs/DDs that require immediate reporting, initial reporting may be done by contacting the study sponsor per the sponsor contact information.

13.2.2. Adverse Event Reporting Requirements

Regulatory reporting of adverse events and device deficiencies will be completed according to local regulatory requirements. Medtronic is also required to report these events to the local regulatory authority based on their requirements. It is the responsibility of the investigator to abide by any additional adverse event and device deficiency reporting requirements stipulated by the IRB/EC responsible for oversight of the study.

Table 7: Adverse Event and Device Deficiency Reporting Requirements

Serious Adverse Events (SAEs)	
Investigator submit to:	
Medtronic	**Europe**: Immediately after the Investigator first learns of the event or of new information in relation with an already reported event. *(ISO 14155 and local law)* **All geographies:** Report to the sponsor, without unjustified delay, all serious adverse events. (ISO 14155:2011)
EC/IRB	**All geographies:** Submit to EC/IRB per local reporting requirement.
Regulatory Authorities	**All geographies:** Submit to regulatory authority per local reporting requirement.
Sponsor submit to:	
EC/IRB	**All geographies:** Submit to EC/IRB per local reporting requirement.
Regulatory Authorities	**All geographies:** Submit to regulatory authority per local reporting requirement.
Serious Adverse Device Effects (SADEs)	
Investigator submit to:	
Medtronic	**Europe:** Immediately after the Investigator first learns of the event or of new information in relation with an already reported event. (ISO 14155 and local law) **All other geographies:** Submit as soon as possible after the Investigator first learns of the event, and per local requirements

EC/IRB	**All geographies:** Submit to EC/IRB per local reporting requirement.
Regulatory authorities	**All geographies:** Submit as soon as possible after the Investigator first learns of the event, and per local requirements
Sponsor submit to:	
EC/IRB	**All geographies:** Submit to EC/IRB per local reporting requirement.
Regulatory authorities	**All geographies:** Submit to regulatory authority per local reporting requirement.
Unanticipated Adverse Device Effects (UADEs) and Unanticipated Serious Adverse Device Effects (USADEs)	
Investigator submit to:	
Medtronic	**US:** Submit as soon as possible, but no later than within 10 working days after the Investigator first learns of the event. (21 CFR 812.150(a)(1)) **Europe:** Immediately after the Investigator first learns of the event or of new information in relation with an already reported event.
EC/IRB	**US:** Submit as soon as possible, but no later than within 10 working days after the Investigator first learns of the event. (21 CFR 812.150(a)(1)) **All geographies:** Submit to EC/IRB per local reporting requirement.
Regulatory authorities	**Europe:** Submit to regulatory authority per local reporting requirement.
Sponsor submit to	
Investigator	**All geographies:** Notification as soon as possible and not later than 10 working days after the sponsor first learns of the effect. (21 CFR 812.150(b)(1))
EC/IRB	**All geographies:** Notification as soon as possible and not later than 10 working days after the sponsor first learns of the effect. (21 CFR 812.150(b)(1))
Regulatory authorities	**US:** Notification as soon as possible to FDA, but not later than 10 working days after the sponsor first learns of the effect. (21 CFR 812.150(b)(1)) **Europe:** Submit to regulatory authorities per local reporting requirement.

Adverse Device Effects	
Investigator submit to:	
Medtronic	**Europe:** Immediately after the Investigator first learns of the effect. *(ISO 14155 and local law)* **All other geographies:** Submit in a timely manner after the Investigator first learns of the effect.
EC/IRB	**All geographies:** Submit to EC/IRB per local reporting requirement.
Regulatory authorities	**All geographies:** Submit to regulatory authority per local reporting requirement.
Sponsor submit to:	
EC/IRB	**All geographies:** Submit to EC/IRB per local reporting requirement.
Regulatory authorities	**All geographies:** Submit to regulatory authority per local reporting requirement.
All other reportable Adverse Events	
Investigator submit to:	
Medtronic	**All geographies:** Submit in a timely manner after the Investigator first learns of the event.
Regulatory authorities	**All geographies:** Submit to regulatory authority per local reporting requirement.
EC/IRB	**All geographies:** Submit to EC/IRB per local reporting requirement.
Sponsor submit to:	
Regulatory authorities	**All other geographies:** Submit to regulatory authority per local reporting requirement.
Device Deficiencies and SADE Potential	
Investigator submit to:	
Medtronic	**Europe:** Immediately after the Investigator first learns of the deficiency or of new information in relation with an already reported deficiency. **All geographies:** Report to the sponsor, without unjustified delay, all device deficiencies that could have led to a serious adverse device effect (ISO 14155:2011)

Regulatory authorities	**All geographies:** Submit to regulatory authority per local reporting requirement.
EC/IRB	**All geographies:** Submit to regulatory authority per local reporting requirement.
Sponsor submit to:	
EC/IRB	**All geographies:** Submit to EC/IRB per local reporting requirement.
Regulatory authorities	**Europe:** Submit to regulatory authorities per local reporting requirement. **All geographies:** Submit to regulatory authority per local reporting requirement.
All Other Device Deficiencies	
Investigator submit to:	
Medtronic	**All geographies:** Submit in a timely manner after the Investigator first learns of the event.
EC/IRB	**All geographies:** Submit to EC/IRB per local reporting requirement.
Regulatory authorities	**All geographies:** Submit to regulatory authority per local reporting requirement.

13.3. Adverse Event Classification

All reported adverse events and device deficiencies will be reviewed by a Medtronic representative. AEs will be classified according to the definitions provided.

Upon receipt of adverse events at Medtronic, a Medtronic representative will review the adverse event/device deficiency for completeness and accuracy and when necessary will request clarification and/or additional information from the Investigator. Medtronic will utilize MedDRA, the Medical Dictionary for Regulatory Activities, to assign a MedDRA term for each adverse event based on the information provided by the investigator

Regulatory reporting of AEs and device deficiencies that could have led to a SADE will be completed according to local regulatory requirements. Refer to Table 7 for a list of required investigator and Medtronic reporting requirements and timeframes. It is the responsibility of the investigator to abide by any additional AE reporting requirements stipulated by the IRB/EC responsible for oversight of the study.

Appendix F contains the foreseeable adverse event List (FAL), which is a list of adverse events related to the system or procedure that have been observed in previous studies and may be experienced by subjects. This list may help to assess if an adverse event is unexpected in nature.

For emergency contact regarding a SAE, contact a clinical study representative immediately (refer to the study contact list provided in the center's study documents binder/investigator site file or refer to the contact information provided on the title page).

Adverse Events and Deaths will be classified according to the standard definitions as outlined below:

Table 8: Adverse Event Classification Responsibilities

What is classified?	Who classifies?	Classification Parameters
Relatedness	Investigator	Cryoablation procedure related, Cryoablation system related, cardiovascular related, AAD related
	Sponsor	Cryoablation procedure related, Cryoablation system related, cardiovascular related
Seriousness	Investigator	SAE
	Sponsor	SAE, UADE/USADE, Device Deficiency with SADE potential
Diagnosis	Investigator	Based on presenting signs and symptoms and other supporting data
	Sponsor	MedDRA term assigned based on the data provided by Investigator
Death Classification	Investigator	Sudden Cardiac, Non-sudden Cardiac, Non-Cardiac, Unknown

13.3.1. Subject Death

All subject deaths must be reported by the Investigator to Medtronic on an adverse event eCRF (AE with outcome of death) soon as possible after the Investigator first learns of the death. There should be one AE with the outcome of death.

13.3.1.1. Death Data Collection

A copy of the death certificate, if available and allowed by state/local law, should be sent to the Medtronic clinical study team. When a death occurs in a hospital, a copy of the death summary report and all relevant hospital records should be sent to the Medtronic clinical study team, if available. If an autopsy is conducted, the autopsy report should also be sent to the Medtronic clinical study team if available and allowed by state/local law. When the death occurs at a remote site, it is the investigative center's responsibility to attempt retrieval of information about the death. In summary, the following data will be collected:

- Date of death
- Detailed description of death
- Cause of death
- Relatedness to device and/or procedure
- Death summary/hospital records (if available and allowed by state/local law)
- Autopsy report (if available and allowed by state/local law)
- Death certificate (if available and/or allowed by state/local law)

13.3.1.2. Death Classification and Reporting

Sufficient information will be required in order to properly classify the subject's death. The Investigator shall classify each subject death per the following definitions:

- Cardiac Death: A death directly related to the electrical or mechanical dysfunction of the heart.
- Sudden Cardiac Death (SCD): Natural death due to cardiac causes, indicated by abrupt loss of consciousness within one hour of the onset of acute symptoms; preexisting heart disease may have been known to be present, but the time and mode of death are unexpected. If time of onset cannot be determined, SCD will alternatively be defined as any unexpected cardiac death occurring out of the hospital or in the emergency room as dead on arrival.
- Non-sudden Cardiac Death: All cardiac deaths that are not classified as sudden deaths, including all cardiac deaths of hospitalized subjects on inotropic support.
- Non-cardiac Death: A death not classified as a cardiac death.
- Unknown Classification: Unknown death classification is intended for use only when there is insufficient or inadequate information to classify the death.

The CEC will review deaths and provide a final adjudication of the primary cause of death and cardiac classification.

Regulatory reporting of subject deaths will be completed according to local regulatory requirements.

13.3.2. Product Complaints

For devices that are market-released, product complaint reporting is applicable. This includes when an AE is related to a market-released device during the study. The reporting of product complaints is not part of the clinical study and should be done in addition to the Adverse Event reporting requirements. Refer to local regulations for reporting requirements.

Product Complaint: Any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness or performance of a medical device that has been placed on the market.

It is the responsibility of the investigator to report all product complaint(s) associated with a medical device distributed by Medtronic, regardless whether they are related to intended use, misuse or abuse of the product. Reporting must be done immediately and via the regular channels for market-released products.

Medtronic will notify the regulatory authorities (e.g. FDA) as applicable for the following incidents immediately upon learning of them:

- Any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labeling or instructions for use which led or might have led to the death or serious deterioration in the state of health of a patient, user, or other person.
- Any technical or medical reason resulting in withdrawal of a device from the market by the manufacturer.
- A serious deterioration in the state of heath includes:
    - Life-threatening illness or injury
    - Permanent impairment of a body function or permanent damage to a body structure
    - A condition necessitating medical or surgical intervention to prevent permanent impairment of a body function or permanent damage to a body structure

The investigator and Medtronic must abide by the reporting requirements shown in Table 7.

14. Data Review Committees

At regular intervals, an independent Clinical Events Committee (CEC) will review and adjudicate all reported adverse events and deaths for subjects participating in the study.

The CEC will consist of a minimum of three (3) non-Medtronic employed physicians that are not participating Investigators for the study, including a CEC chairperson.

Medtronic personnel may facilitate and participate in a CEC meeting but will be non-voting members.

For adverse events and deaths reviewed by the CEC, Medtronic will provide the CEC with the Investigator's description and classification. The CEC is responsible for reviewing the Investigator's assessment and supportive documentation (when available), reviewing applicable definitions, and determining final classifications for all adjudication parameters. Additionally, the CEC will provide an adjudication of the death classification for all reported deaths including primary cause of death and cardiac classification.

If the CEC disagrees with the Investigator's classification of the event, the rationale will be provided to the Investigator. If the Investigator agrees with the CEC's adjudication, the eCRF documenting the event will be updated accordingly.

If the Investigator does not agree with the CEC's adjudication classification, both determinations will be provided within the final report; however, the CEC's adjudication will be used for data analysis. The disagreement will also be included in reporting to IRB and regulatory authorities, if required.

15. Statistical Design and Methods

Medtronic employees will perform all statistical analyses.

Additionally, a separate Statistical Analysis Plan (SAP) will be developed to further describe statistical methods, pre-specified data handling rules (including how missing data will be handled), and pre-specified analyses, including subgroup analyses, that will be included in study reports (e.g. PMA report, final study report). Any deviation from the pre-specified statistical analyses will be noted in the study report.

The SAP will include a comprehensive description of the statistical methods and analyses to be included in reports that include analysis of endpoints. Any change to the data analysis methods described in the CIP will require an amendment to the CIP only if it changes a principal feature of the CIP. Any other change to the data analysis methods described in the CIP, and the justification for making the change, will be described in the clinical study report.

Additional exploratory analyses of the data may be conducted as deemed appropriate.

All objectives will be analyzed once all treated subjects complete the 12 month follow-up visit, or have exited the study. A final report will be completed after all subjects complete the final follow-up visit, or have exited the study. No interim analyses are planned.

The primary analysis will be conducted using a modified intent-to-treat protocol; all subjects for whom either AAD or cryoballoon ablation therapy is initiated will be analyzed according to their randomization status. Subjects who withdraw consent between randomization and initiation of therapy will be excluded from the primary efficacy analysis.

15.1. Primary Efficacy Objective

Demonstrate the superiority of cryoballoon ablation as compared to AAD therapy in terms of the rate of freedom from AF/AT/AFL in a non-drug refractory paroxysmal AF population.

15.1.1. Hypothesis

The hypothesis test used in assessment of the primary efficacy objective is that the proportion of subjects with treatment success at 12 months is greater in subjects randomized to cryoballoon ablation compared to subjects randomized to AAD therapy.

The following hypothesis will be tested in a two-sided test with $\alpha = 0.05$:

H_0: $\pi_{cryo} = \pi_{AAD}$

H_a: $\pi_{cryo} \neq \pi_{AAD}$

Where π_{cryo} and π_{AAD} are the proportion of treatment successes at 12 months in the modified intention-to-treat cohorts of the cryoballoon ablation and AAD groups, respectively.

15.1.2. Endpoint Definition

A treatment success is the opposite of a treatment failure.

A subject is considered a treatment failure if he/she experiences any of the following:

- Acute procedural failure (defined in section 5.1.4.1; treatment arm only)
- Documented AF/AT/AFL on ambulatory monitoring/12-lead ECG after the 90 day post-ablation blanking period (treatment arm)/AAD optimization period (control arm).
    - Minimum of 30 seconds on ambulatory monitoring or 10 seconds on 12-lead ECG.
    - Note: Documented occurrence and treatment of typical right-sided cavotricuspid isthmus dependent atrial flutter is not considered a failure if confirmed by entrainment maneuvers during EP testing.
- Any subsequent AF surgery or ablation in the left atrium.
- Any subsequent cardioversion after the 90 day post-ablation blanking period (treatment arm)/AAD optimization period (control arm).
- Class I or III antiarrhythmic drug (or sotalol) use after the 90 day blanking period (treatment arm only).

The AAD optimization period is defined as the first 90 days after AAD initiation (control arm). The blanking period is defined as the first 90 days after the index ablation procedure (treatment arm). Recurrences of atrial arrhythmias during the AAD optimization/blanking periods will not be counted in the determination of the first clinical failure for the primary endpoint. Within the 90 day AAD optimization period and 90 day post-ablation blanking period, recurrent arrhythmias can be managed with medications or cardioversions.

15.1.3. Performance Requirements

If a two-sided log-rank test shows the difference in 12-month success rates to be less than the pre-specified alpha of 0.05, the null hypothesis (that cryoballoon ablation has similar 12-month efficacy rates compared to AAD therapy) will be rejected in favor of the alternative hypothesis (that 12-month success

rates for subjects treated with cryoballoon ablation is greater than for those treated with AAD's), demonstrating the superiority of the cryoballoon ablation procedure for this endpoint.

15.1.4. Rationale for performance criteria

The performance requirement for this objective involves showing superior treatment efficacy rates through 12 months in a randomized study against the current standard of care, in a population of paroxysmal AF patients. The randomized nature of the study will provide the highest level of evidence that, in the event a statistically significant result is attained, that the treatment is indeed responsible for the difference in 12-month success.

15.1.5. Analysis Methods

The probability of a subject achieving success at 12 months (365 days) will be estimated using Kaplan-Meier survival analysis. The standard error will be approximated using Greenwood's formula. A two-sided 95% log-log confidence interval for the probability will be constructed. A two-sided log rank test with $\alpha = 0.05$ will be used to assess whether the failure rate differs between treatment groups.

Day 0 is defined as either the day of the index cryoablation procedure or the day in which AAD drug therapy is initiated. For subjects with treatment failure, the survival date will be set to the date of the treatment failure. For subjects without treatment failure through 12 months, those subjects will be censored at the last study contact date recorded on a CRF, which may include the last study visit, the exit date, or death date. If a subject without a treatment failure is lost to follow-up, the censoring date will be set to the last recorded study visit date. If treatment failure occurs on the day of index treatment, survival time will be set to 0.5 days.

If an occurrence of documented AF/AT/AFL resulted from rhythm monitoring that was initiated at the 12-month visit, then the date of occurrence used in the Kaplan-Meier analysis will be the minimum of 365 days from the cryoballoon ablation procedure/date of AAD initiation or the actual date of occurrence. This allows counting of all AF/AT/ AFL events found at the 12-month follow-up, even if the follow-up occurred after 365 days post-ablation.

The survival curves from 0 to 12 months will be presented for both treatment arms.

15.1.6. Sample Size

Sample size assumptions are:

- Two-sided chi-squared test
- Alpha=0.05
- AAD 12-month success rate = 45%
- Cryoballoon ablation group 12-month success rate = 69.9%
- Power>90%
- Attrition from enrollment to 1 year = 10%

The above assumptions require 87 subjects per arm with data, or 174 total subjects. Adding in 10% attrition brings the overall enrollment sample size to 194 for this objective. Note that a log-rank test will be used for the primary efficacy analysis, but the more conservative chi-squared test was used for sample size estimation.

15.1.7. Determination of Patients/Data for Analysis

A modified intention-to-treat protocol will be utilized for the primary efficacy analysis: all subjects for whom either AAD or cryoballoon ablation therapy is initiated will be analyzed according to their randomization status. Subjects who withdraw consent between randomization and initiation of therapy will be excluded from the primary efficacy analysis.

15.2. Primary Safety Objective

Demonstrate an acceptable safety profile of the cryoballoon ablation procedure as a first line therapy in a non-drug refractory paroxysmal AF population.

15.2.1. Hypothesis

The following hypothesis will be tested in a one-sided test with $\alpha = 0.025$:

H_0: $P_s \geq 12\%$

H_a: $P_s < 12\%$,

where P_s is the probability of a safety event in subjects from the cryoballoon arm.

15.2.2. Endpoint Definition

A primary safety event is defined as a serious procedure-related or cryoablation system-related adverse event that includes any of the following:

- TIA within 7 days
- Cerebrovascular accident within 7 days
- Major bleeding that requires transfusion or results in a 20% or greater fall in hematocrit (HCT) within 7 days
- Development of a significant pericardial effusion within 30 days. A significant pericardial effusion is one that results in hemodynamic compromise, requires elective or urgent pericardiocentesis, or results in a 1-cm or more pericardial effusion as documented by echocardiography.
- Symptomatic PV stenosis within 12 months; accompanied by one of the following: 50%-75% reduction in diameter of the pulmonary vein, with symptoms not explained by other conditions; OR >75% reduction in diameter of the pulmonary vein
- MI within 7 days
- PNI unresolved at 12 months
- AE fistula within 12 months
- Major vascular complication that requires intervention, prolongs the hospital stay, or requires hospital admission (within 7 days).

15.2.3. Performance requirements

If the upper bound of the two-sided 95% confidence interval of the safety event rate in cryoballoon arm subjects is <12%, this objective will be considered met.

15.2.4. Rationale for Performance Criteria

The safety endpoint definition and performance goal (PG) of 12% for safety events were based on previous and current Medtronic cryoballoon ablation catheter studies, as well as based on feedback from FDA staff.

A primary safety event rate of 3.1% was observed in the STOP AF trial. The 2016 Annual Report for the STOP AF PAS study reports a 12 month safety event rate of 2.3%. For this study, the safety event definition has been expanded according to FDA guidance, and certain events (e.g., symptomatic PV

stenosis from 50 – 75%, cardiac perforation/tamponade from 8 – 30 days after the procedure) not included in the two previous studies will be included. Based on the STOP AF trial and STOP AF PAS adverse event data and the expanded safety event definition, it is estimated that the current study will have a safety rate of 4.0%.

The STOP AF pivotal study and STOP AF Post-Approval Study (STOP AF PAS) both set PG requirements of 14.8%. With an estimated 4% safety rate, a PG of 12% provides stricter criteria than used in prior cryoballoon studies, in order to account for differences in the study populations.

Additionally, the STOP AF Pivotal trial reported that 8.5% of subject's experienced a Major Atrial Fibrillation Events (MAFEs) in the AAD arm (Packer et al., 2013). A large systematic review also reported that withdrawals from AADs due to adverse events averaged 16.2% for Class I AADs and 11.4% for Class III AAD's (Lafuente-Lafuente, Valembois, et al. 2015). Therefore the performance criteria established in this study is appropriate for demonstrating an acceptable risk-benefit in this drug-naïve PAF population.

15.2.5. Analysis Methods

The probability of a safety event within 12 months will be estimated using Kaplan-Meier survival analysis. Greenwood's formula will be used to approximate the standard error of the survival curve, and a two-sided log-log confidence interval at 12 months will be reported.

Day 0 is defined as the day of the index cryoablation procedure. For subjects with a safety event, the survival date will be set to the date of the safety event. For subjects without a safety event, censoring will occur at the last study contact date with a corresponding CRF (i.e., the last study visit, exit date or death). If a subject without a safety event is lost to follow-up they will be censored on the date of the last study visit.

Any subsequent ablations a subject may have after day 0 will not reset their survival time; the date of the index procedure will remain as day 0 for purposes of the primary safety analysis. Safety events related to repeat ablation procedures occurring up to 365 days after the index cryoablation date will be considered as having met criteria for the primary safety endpoint, and will be counted as failures for this analysis.

15.2.6. Sample Size

Sample size assumptions are:

- One-sample, one-sided exact binomial test
- Alpha = 0.025
- Cryoballoon ablation 12-month safety rate = 4%
- PG = 12%
- Attrition from enrollment to 1 year = 10%

Under these conditions, 210 enrolled subjects are required at 1:1 randomization and 10% attrition in order to expect 94 randomized and analyzable subjects at 12-month follow-up in the cryoballoon ablation arm, which affords 80% power for a one-sided binomial test with $\alpha = 0.025$.

15.2.7. Determination of Patients/Data for Analysis

All subjects randomized to the cryoablation arm and have the Arctic Front Advance Cardiac CryoAblation Catheter inserted into vasculature will be included.

Subjects randomized to the AAD arm who receive a cryoablation procedure during follow-up will not be included in the primary safety analysis; however, safety events occurring in these subjects will be reported into the study database and summarized.

15.3. Secondary Objectives

Two secondary objectives will be evaluated to gain additional information about the performance of the Arctic Front Advance Cardiac CryoAblation catheter, with four hypotheses to be tested.

Secondary Objective #1:

Assess changes in quality of life between baseline and 12 months in the cryoballoon ablation arm. There are two hypotheses tested in the objective, with separate hypothesis tests for (1) the difference in composite scores from the AFEQT questionnaire taken at baseline and 12 month visits, and (2) for the difference in composite scores for the EQ-5D questionnaire taken at baseline and 12-month visits.

Secondary Objective #2:

Compare health care utilization between the treatment and control arms. There are two hypotheses tested in the objective, with separate hypothesis tests for: (1) the rate of total health care utilization events (cardiovascular-related hospitalizations, emergency room visits, or unscheduled office visits) over 12 months, and (2) the rate of cardioversions (electrical or pharmacological) over 12 months.

Testing for these objectives will be performed if the primary objectives are met. A Hochberg multiple testing procedure will be utilized to maintain an overall type I error rate of 0.05 for the four hypotheses being tested among the two secondary objectives.

The Hochberg procedure is a stepwise procedure and will be implemented as follows:

The four hypotheses will be defined as H(1), H(2), H(3), and H(4). For each of the hypotheses, p-values will be calculated and sorted $p(1) < p(2) < p(3) < p(4)$. The decision rule to accept or reject each hypothesis will follow the step-up algorithm, where $\alpha=0.05$:

Step 1: If $p(4) \geq \alpha$, accept H(4) and go to Step 2, otherwise reject all hypotheses and stop

Step 2: If $p(3) \geq \alpha/2$, accept H(3) and go to Step 3, otherwise reject H(3), H(2) and H(1) and stop

Step 3: if $p(2) \geq a/3$, accept H(2) and go to Step 4, otherwise reject H(2) and H(1) and stop

Step 4: If $p(1) < a/4$, reject H(1); otherwise accept H(1)

15.3.1. Atrial Fibrillation Effect on Quality-of-Life (AFEQT)

15.3.1.1. Hypothesis

The following hypothesis will be tested in a two-sided test:

Ho: $AFEQT_{month12} = AFEQT_{baseline}$
Ha: $AFEQT_{month12} \neq AFEQT_{baseline}$,

Where $AFEQT_{baseline}$ is the score from the AFEQT assessed at the baseline visit, and $AFEQT_{month12}$ is the composite score from the AFEQT assessment from the 12-month follow-up.

15.3.1.2. Endpoint Definition

The AFEQT questionnaire will be utilized for this objective. The questionnaire is an atrial fibrillation specific health-related quality of life questionnaire to assess the impact of AF on a subject's life. The overall score ranges from 0 – 100, with 0 corresponding to complete disability and 100 corresponding to no disability. The absolute difference between each subject's baseline and 12 month scores is the endpoint of interest.

15.3.1.3. Analysis Methods

The difference in mean AFEQT scores will be assessed utilizing a paired t-test.

15.3.1.4. Performance Criteria

If the p-value from the two-sample t-test procedure is less than the alpha level determined by the Hochberg procedure described above, the objective will be considered met.

15.3.1.5. Rationale for Performance Criteria

If this analysis shows that scores from the AFEQT, a validated instrument for measuring quality of life in subjects with atrial fibrillation (Spertus, et al. 2011), are significantly higher 12 months after the procedure compared to before the procedure, it will show a documented association between the cryoballoon ablation procedure and QoL improvement in a non-drug refractory paroxysmal AF population. . While this hypothesis test will not be between randomized groups, in the context of a secondary objective that will only be tested if efficacy has been established, such results would provide evidence of a QoL improvement in cryoballoon ablation-treated patients.

15.3.1.6. Determination of Subjects/Data for Analysis

All subjects randomized to the cryoballoon ablation group who have completed both baseline and 12-month questionnaires will be included and analyzed.

Comparison to the AAD arm is not planned as it is expected that a large percentage of AAD arm subjects will have a cryoballoon procedure during the 12 months of follow-up. Having a cryoballoon procedure prior to 12 months will bias the AAD arm's 12-month QOL results.

15.3.1.7. Additional analyses

The AFEQT questionnaire has three subscale scores, Daily Activities Subscale, Treatment Concern, and Treatment satisfaction. Each subscale ranges from 0 – 100, where 0 corresponds to low quality-of-life and 100 corresponds to high quality of life.

Change in AFEQT subscale score is defined as 12-month AFEQT subscale score minus baseline AFEQT subscale score. A two-sided 95% confidence interval will be calculated based on the t-distribution.

15.3.2. EQ-5D Questionnaire

15.3.2.1. Hypothesis

The following hypothesis will be tested in a two-sided test:

Ho: $EQ\text{-}5D_{month12} = EQ\text{-}5D_{AAD}$
Ha: $EQ\text{-}5D_{month12} \neq EQ\text{-}5D_{AAD}$

Where $EQ\text{-}5D_{month12}$ is the mean composite EQ5D score from subjects assessed at the 12 month visit, and $EQ\text{-}5D_{baseline}$ is the mean composite EQ-5D score for at baseline.

15.3.2.2. Endpoint Definition

The Euroqol EQ-5D questionnaire (which consists of a 5-question survey and a visual analog scale indicating the subject's overall health) will be utilized for this objective. Composite scores will be indexed against a US reference population. (Shaw, Johnson and Coons 2004)

15.3.2.3. Analysis Methods

Change in EQ-5D composite score is defined as 12-month EQ-5D score minus baseline EQ-5D score. Differences in mean EQ-5D scores between visits will be assessed utilizing a paired t-test. A two-sided 95% confidence interval will be calculated based on the t-distribution.

15.3.2.4. Performance criteria

If the p-value from the paired t-test is less than the alpha level determined by the Hochberg procedure described above, the objective will be considered met.

15.3.2.5. Rationale for Performance Criteria

If this analysis shows that EQ-5D scores are significantly higher after 12-months follow-up compared to baseline in cryoballoon-treated subjects, it will provide evidence of an association between cryoballoon ablation and a general QoL increase (as measured by a validated instrument) that may or may not be causal. While this hypothesis test will not be between randomized groups, in the context of a secondary objective that will only be tested if efficacy has been established, the evidence provided is stronger than if it were just performed in an isolated pre-post comparison.

15.3.2.6. Determination of Subjects/Data for Analysis

All cryoballoon ablation arm subjects who have completed both baseline and 12-month questionnaires will be included and analyzed.

Comparison to the AAD arm is not planned as it is expected that a large percentage of AAD arm subjects will have a cryoballoon procedure during the 12 months of follow-up. Having a cryoballoon procedure prior to 12 months will bias the AAD arm's 12-month QoL results.

15.3.3. Cardiovascular hospitalizations, ED and unscheduled office visits

15.3.3.1. Hypothesis

The following hypothesis will be tested.

H_0: $\theta_{cryo} = \theta_{AAD}$

H_a: $\theta_{cryo} \neq \theta_{AAD}$,

where θ_{cryo} and θ_{AAD} are the 12-month rates of cardiovascular HCU events in the cryoballoon ablation and AAD arms, respectively.

15.3.3.2. Endpoint Definition

Healthcare utilization (HCU) events for this objective are defined as cardiovascular-related hospitalizations, cardiovascular-related emergency department visits, or cardiovascular-related unscheduled office visits occurring within 12 months after the index ablation (cryo arm) or the initiation of therapy (AAD arm). Events occurring >365 days after initiation of treatment but before the 12-month visit will be included.

15.3.3.3. Analysis Methods

The probability of a subject achieving freedom from HCU events (defined above) at 12 months will be estimated using Kaplan-Meier survival analysis. The standard error will be approximated using Greenwood's formula. A two-sided 95% log-log confidence interval for the probability at 12 months will be constructed. A two-sided log rank test will be used to assess whether the HCU event rate differs between treatment groups.

Day 0 is defined as day of the index cryoablation procedure or the day in which drug therapy is initiated. For subjects with treatment failure, the survival date will be set to the date of the first HCU event. For subjects without any HCU events through 12 months, those subjects will be censored at the last study contact date recorded on a CRF which may include the last study visit, the exit date or the date of death. If a subject without any HCU events is lost to follow-up, the censoring date will be set to the last known study visit date. For HCU events occurring on the day of index treatment, survival time will be set to 0.5 days.

The survival curve from 0 to 12 months will be presented for both treatment arms. HCU events will also be summarized by type and treatment group.

15.3.3.4. Performance Requirements

If the p-value from two-sided log-rank test is less than the alpha level determined by the Hochberg procedure described above, the objective will be considered met.

15.3.3.5. Rationale for Performance Requirements

If the test specified above indicates a statistically significant increase in the time to the first HCU event between cryoballoon ablation and AAD-treated subjects, this is sufficient evidence to say that the treatment has a lower rate of healthcare utilization within a year of treatment initiation, due to the randomized and intention-to-treat nature of the comparison.

15.3.3.6. Determination of Subjects/Data for Analysis

The modified intent-to-treat cohort will be utilized. All subjects who initiate either AAD therapy or cryoballoon ablation will be analyzed according to the group to which they were randomized.

15.3.4. Cardioversions

15.3.4.1. Hypothesis

The following hypothesis will be tested with a two-sided test.

H_0: $\gamma_{cryo} = \gamma_{AAD}$

H_a: $\gamma_{cryo} \neq \gamma_{AAD}$,

where γ_{cryo} and γ_{AAD} are the 12-month rates of cardioversion (either electrical or pharmacological) in the cryoballoon ablation and AAD arms, respectively.

15.3.4.2. Endpoint Definition

A cardioversion event is defined as an electrical or pharmacological cardioversion post index ablation discharge for the treatment arm, and post AAD initiation for the AAD arm

15.3.4.3. Analysis Methods

The probability of a subject achieving freedom from cardioversion (defined above) at 12 months (365 days) will be estimated using Kaplan-Meier survival analysis. The standard error will be approximated using Greenwood's formula. A two-sided 95% log-log confidence interval for the probability at 12 months will be constructed. A two-sided log rank test, with significance level determined by the Hochberg procedure described above, will be used to assess whether the cardioversion rate differs between treatment groups.

Day 0 is defined as the day of the index cryoablation procedure or the day in which drug therapy is initiated. For subjects with at least one cardioversion, the survival date will be set to the date of the first cardioversion. For subjects without any cardioversions through 12 months, those subjects will be censored at the last study contact date recorded on a CRF which may include the last study visit, the exit date, or the date of death. If a subject without any cardioversions is lost to follow-up, the censoring date will be set to the last known study visit date. For cardioversions occurring on the day of index treatment, survival time will be set to 0.5 days.

The survival curve from 0 to 12 months will be presented for both treatment arms. Counts of all cardioversions administered over 12 months will also be summarized.

15.3.4.4. Performance Requirements

If the p-value from two-sided log-rank test is less than the alpha level determined by the Hochberg procedure described above, the objective will be considered met.

15.3.4.5. Rationale for Performance Criteria

If the test specified above indicates a statistically significant increase in the time to the first cardioversion between cryoballoon ablation and AAD-treated subjects, this is sufficient evidence to say that the treatment has a lower rate of cardioversions within a year of treatment initiation, due to the randomized and intention-to-treat nature of the comparison.

15.3.4.6. Determination of Subjects/Data for Analysis

The modified intent-to-treat cohort will be utilized. All subjects who initiate either AAD therapy or cryoballoon ablation will be analyzed according to the group to which they were randomized in the assessment of this objective.

15.4. Ancillary Objectives

Ancillary objectives been defined to provide additional information about the performance of the Arctic Front Advance Cardiac CryoAblation Catheter. No hypotheses are defined for regulatory or labeling purposes.

15.4.1.

15.4.2.

[redacted]

15.4.3. [redacted]

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15.4.4. [redacted]

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15.4.5. [redacted]

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16. Ethics

16.1. Statement(s) of Compliance

The study will be conducted in compliance with international ethical and scientific quality standards, known as good clinical practice (GCP). GCP includes review and approval by an independent Institutional Review Board (IRB)/ Ethics Committee (EC) before initiating a study, continuing review of an ongoing study by an IRB/EC, and obtaining and documenting the freely given informed consent of a subject before initiating the study.

The study was designed to reflect the GCP principles outlined in ISO 14155:2011 and other international clinical requirements outlined below. These include the protection of the rights, safety and well-being of human subjects, controls to ensure the scientific conduct and credibility of the clinical investigation and the definition of responsibilities of the sponsor and Investigators. In accordance with ISO standard, the sponsor shall avoid improper influence on, or inducement of, the subject, monitor, any Investigator(s) or other parties participating in or contributing to the clinical investigation. All Investigators shall avoid improper influence on or inducement of the subject, sponsor, monitor, other Investigator(s) or other parties participating in or contributing to the clinical investigation. The ISO standard also informed study design in the areas of device deficiency reporting and risk evaluation, with the exception (to Section 6.4 of the ISO standard) that only those Adverse Events (AEs) which are cardiovascular related, serious (regardless of relatedness), AAD related, cryoablation system related and/or procedure related will be collected. This ensures any AEs which could potentially be relevant will be collected. There is a second exemption (to Section 9.8 of the ISO standard) that device accountability will not be performed in Europe and only upon package opening in the US.

The study will be conducted according to the CIP, federal, national and local laws, regulations, standards, and requirements of the countries/geographies where the study is being conducted. In Europe, the study will also be conducted in accordance with the Declaration of Helsinki 2013. For all geographies, the principles of the Declaration of Helsinki have been implemented through the patient informed consent (IC) process, IRB/EC approval, study training, clinical trial registration, preclinical testing, risk-benefit assessment and publication policy.

Ultimately, all centers in all geographies will follow and comply with:

- Principles of Declaration of Helsinki (including privacy and data protection laws), or the laws and regulations of each participating country, whichever affords greater protection for the study subjects
- 21 CFR Part 11 (Electronic Records, Electronic Signatures)
- 21 CFR Part 54 (Financial Disclosure by Clinical Investigators)
- The procedures described with in this CIP
- Local Ethics Board requirements

All participating geographies will make study data available to the regulatory body such as FDA or competent authority if the regulatory body deems an onsite inspection necessary. The regulatory body will be able to inspect records at clinical centers around the world to resolve any uncertainties about whether the study was conducted in accordance with good clinical practice.

In addition to the regulatory requirements outlined above, the study will be conducted in compliance with relevant local laws. These include but are not limited to:

- In the United States, US FDA 21 CFR Parts
    - 50: Protection of Human subjects,
    - 56: Institutional Review Boards
    - 812: Investigational Device Exemptions
- In Europe, Declaration of Helsinki 2013, the Competent Authority requirements, the Medical Device Directive (MDD) 93/42/EEC and ISO 14155:2011 with the exceptions stated earlier in this Section

The study will be publicly registered prior to first enrollment in accordance with the 2007 Food and Drug Administration Amendments Act (FDAAA) and Declaration of Helsinki on http://clinicaltrials.gov (PL 110 85, Section 810(a)).

Approval of the Clinical Investigation Plan (CIP) is required from the following groups prior to any study procedures at a study center:

- US Food and Drug Administration (FDA) or regulatory authority
- Medtronic
- Principal Investigators (where required by local law)
- An independent IRB/EC

Similarly, approval of subsequent revisions to the CIP is required at each study center from the above mentioned groups prior to implementation of the revised CIP at that center.

Medtronic maintains appropriate clinical study liability insurance coverage as required under applicable laws and regulations and will comply with applicable local law and custom concerning specific insurance coverage. If required, a clinical insurance statement/certificate will be provided to the IRB/EC.

The study is conducted in multiple countries, therefore reimbursement and indemnification will be addressed on a country specific basis in the study documents and center Clinical Trial Agreements.

17. Study Administration

17.1. Role of the Sponsor Representatives

Sponsor representatives may provide support as required for the study under supervision of the Principal Investigator, including:

- Provide study training relevant and pertinent to the involvement of personnel conducting study activities and investigator responsibilities
- Technical support at the ablation procedure under the supervision of a study investigator, but no data entry, shall be performed by Medtronic personnel or their representatives at sites
- Monitoring and auditing activities

17.2. Monitoring

It is the responsibility of Medtronic to ensure proper monitoring of this clinical study. Trained Medtronic personnel or delegates appointed by Medtronic may perform study monitoring at the study center in order to ensure that the study is conducted in accordance with the CIP, the Clinical Trial Agreement, and applicable regulatory and local requirements. Medtronic, or delegates, must therefore be allowed direct access to the subjects' case histories (clinic and hospital records, and other source data/documentation) upon request as per the IC Form, Research Authorization (where applicable) and Clinical Trial Agreement. The Principal Investigator should also be available during monitoring visits.

Frequency of monitoring visits will occur based on subject enrollment, duration of the study, study compliance, number of adverse events, number of deviations, findings from previous monitoring visits and any suspected inconsistency in data that requires investigation. Regulatory documents (e.g., IRB/EC approval letters, etc.) may be reviewed at each study center. Monitoring for the study may include, but are not limited to, site initiation visits, interim monitoring visits, and closeout visits, and will be done in accordance with the study-specific monitoring plan. The extent of source data verification will be specified in the study-specific monitoring plan.

Monitoring visits will be conducted periodically to assess site study progress, the investigator's adherence to the Clinical Investigation Plan, regulatory compliance including but not limited to IRB/MEC approval and review of the study, maintenance of records and reports, and review of source documents against subject CRFs and for unreported adverse events. In Europe, calibration and maintenance of study equipment will be monitored. Monitors facilitate site regulatory and study compliance by identifying findings of non-compliance and communicating those findings along with recommendations for preventative/corrective actions to site personnel. Findings and non-compliance will also be communicated to study personnel via a monitoring follow-up letter. Monitors may work with study personnel to determine appropriate corrective action recommendations and to identify trends within the study or at a particular center.

17.3. Data Management

Data will be collected via an electronic data management system for clinical studies. CRF data will be stored in a secure, password-protected database which will be backed up nightly. Data will be reviewed using programmed and manual data checks. Data queries will be made available to centers for resolution. The Investigator must approve the completed CRFs and the Investigator, or authorized designee, must complete CRFs and make CRF corrections.

Data collected by ambulatory monitoring and 12-lead ECGs will be managed and over-read by a core lab. Final classification of recurrent AF/AT/AFL will be stored in the study database.

Study management reports may be generated to monitor data quality and study progress. At the end of the study, the data will be frozen and will be retained indefinitely by Medtronic.

All records and other information about subjects participating in this study will be treated as confidential. Data will be transferred and processed by Medtronic or a third party designated by Medtronic in a key coded form, unless it's impossible to make it anonymous, for instance, where the subject's name cannot be removed from the data carrier, such as fluoroscopy images. In the case that de-identifying is impossible or involves a disproportionate effort, files containing personal data of subjects shall only be made accessible to authorized persons (secured role-based access).

17.4. Direct Access to Source Data/Documents

The sponsor or a regulatory authority may audit or inspect the study site to evaluate the conduct of the study. The clinical investigator(s)/institution(s) shall allow study related monitoring, audits, IRB review and regulatory inspection by providing direct access to source data/documents. If direct access is not feasible, certified copies shall be provided to the sponsor or regulatory authority.

17.5. Confidentiality

All records and other information about subjects participating in this study will be treated as confidential. See sections 17.3 and 17.4 for further information.

17.6. CIP Amendments

Approval of subsequent revisions to the CIP is required at each study center from the following groups prior to implementation of the revised CIP at the center:

- Medtronic
- Principal Investigators (where required by local law)
- Geography-specific regulatory authorities (if regulatory approval is required)
- An independent EC or IRB

If a CIP amendment occurs, center personnel will need to be re-trained as necessary, and will need to submit any changes to their IRB/EC as required by the committee. CIP amendments will also be reported to and approved by the FDA.

17.7. Record Retention and Reports

Medtronic records and reports will be maintained in a password-protected document management system, and paper documents (where applicable) will be stored in stored in secured file cabinets at Medtronic during the course of this study.

After closure of the study Medtronic will archive records and reports indefinitely.

17.7.1. Investigator Records

The investigator is responsible for the preparation and retention of the records cited below. All of the below records, with the exception of case history records and case report forms, should be kept in the Investigator Site File (i.e., the study binder provided to the investigator) or Subject Study Binder. CRFs may be maintained and signed electronically within the electronic data capture system during the trial. The following records are subject to inspection and must be retained for a period of two years (or longer as local law or hospital administration requires) after the date on which the investigation is terminated.

- All correspondence between the IRB/EC, sponsor, monitor, FDA and/or other regulatory bodies, and/or the investigator that pertains to the investigation, including required reports
- Subjects' case history records, including:
    - Signed and dated Informed Consent Form
    - Observations of adverse events/adverse device effects
    - Medical history
    - Procedure and follow-up data
    - Documentation of the dates and rationale for any deviation from the protocol
- Reports of Adverse Events
- Signed and dated CRFs
- Blank case report forms (Europe only)
- Subject screening logs (if used) and subject identification logs (Europe only)
- Randomization list
- List of investigation centers
- All approved versions of the CIP, ICF, and Investigator's Brochure/Report of Prior Investigation Summary
- Signed and dated Clinical Trial Agreement and Investigator Statement
- Financial Disclosure of Investigators
- Current curriculum vitae (signed and dated in Europe) of all participating Investigators and key members of investigation center team (Europe only)
- Documentation of delegated tasks
- IRB/EC approval documentation including written information that the investigator or other study staff, when member of the IRB/EC, did not participate in the approval process. Approval documentation must include the IRB/EC composition, in Europe and where required by local law.
- Regulatory authority notification, correspondence and approval, where required by local law.
- Study training records for center staff
- Insurance certificates (where required by the IRB/EC)
- Any other records that FDA or regulatory authorities require to be maintained
- Final Report of the clinical investigation prepared and distributed by the sponsor
- Final Investigator Report prepared by center and submitted to their IRB
- Final Clinical Study Report, including the statistical analysis

17.7.2. Investigator Reports

The Investigator is responsible for the preparation (review and signature) and submission to the sponsor of all case report forms, adverse events, device deficiencies, deaths, and any deviations from the clinical

investigation plan. If any action is taken by an IRB/EC with respect to this clinical study, copies of all pertinent documentation must be forwarded to Medtronic in a timely manner. Reports are subject to inspection and to the retention requirements as described above for investigator records.

The investigator shall prepare and submit in a complete, accurate and timely manner the reports listed in this section.

Table 9: Investigator reports applicable for all geographies per Medtronic Requirements

Report	Submit to	Description/Constraints
Withdrawal of IRB/EC approval	Sponsor and Relevant authorities	The Investigator must report a withdrawal of approval by the reviewing IRB/EC of the Investigator's part of the investigation within 5 working days.
Study deviations	Sponsor and IRB/EC	Any deviation from the clinical investigation plan shall be recorded together with the explanation of the deviation. Notice of deviations from the CIP to protect the life or physical wellbeing of a subject in an emergency shall be given as soon as possible, but no later than 5 working days after the emergency occurred. Except in such emergency, prior approval is required for changes in the plan or deviations.
Final report	Sponsor IRBs/ECs Relevant Authorities	This report must be submitted within 3 months of study completion or termination.
Refer to Section 13 for adverse event, complaint, and device deficiency reporting.		

Table 10: Additional Investigator reports applicable to the United States

Report	Submit to	Description/Constraints
Withdrawal of IRB/EC approval	Sponsor	The Investigator must report a withdrawal of approval by the reviewing IRB/EC of the Investigator's part of the investigation within 5 working days. (21 CRF 812.150 (a)(2)).
Progress report	Sponsor and IRB/EC	The Investigator must submit this report to the sponsor and IRB at regular intervals, but in no event less than yearly. (21 CFR 812.150 (a)(3)).
Study deviations	Sponsor and IRB/EC	Notice of deviations from the clinical investigation plan to protect the life or physical wellbeing of a subject in an emergency shall be given as soon as possible, but no later than 5 working days after the emergency occurred. Except in such emergency, prior approval is required for changes in the plan or deviations. If the deviation may affect the scientific soundness of the plan or the rights, safety and welfare of the subjects, the deviation must be approved by Medtronic, the IRB/EC, and the FDA/applicable regulatory authorities. If the deviation does not affect these issues then only Medtronic must approve it. (21 CFR 812.150(a)(4))
Failure to obtain Informed Consent Form prior to investigational device use	Sponsor and IRBs/ECs	If an Investigator uses a device without obtaining a signed Informed Consent Form, the Investigator shall report such use within 5 working days after device use. (21 CFR 812.150(a)(5))
Final report	Sponsor IRBs/ECs Relevant Authorities	This report must be submitted within 3 months of study completion or termination of the investigation or the Investigator's part of the investigation. (21 CFR 812.150(a)(6))
Other	IRB/EC and FDA	An investigator shall, upon request by a reviewing IRB, FDA or any other regulatory agency, provide accurate, complete, and current information about any aspect of the investigation. (21 CFR 812.150(a)(7))

Table 11: Investigator reports applicable to Europe

Report	Submit to	Description/Constraints
Withdrawal of IRB/EC approval	Sponsor	Report if required by local law.
Progress report	Sponsor and IRB/EC	Provide if required by local law or IRB/EC.
Study deviations	Sponsor and IRB/EC	Any deviation from the CIP shall be recorded together with an explanation for the deviation. Deviations shall be reported to the sponsor who is responsible for analyzing them and assessing their significance. Note: When relevant, ethics committees, competent authorities or the appropriate regulatory bodies should be informed. (ISO 14155:2011)
Failure to obtain informed consent	Sponsor and IRBs/ECs	Informed consent shall be obtained in writing and documented before a subject is enrolled into the clinical investigation. (ISO 14155:2011)

17.7.3. Sponsor Records

Medtronic shall maintain the following accurate, complete, and current records:

- All correspondence which pertains to the investigation
- Signed Investigator Trial Agreements, financial disclosure of Investigators, and current signed and dated (Europe only) curriculum vitae of Principal Investigator and key members of the investigator center team (as required by local law), and Delegated Tasks List
- All approved versions of the ICF, and other information provided to the subjects and advertisements, including translations.
- All approved versions of the Clinical Investigation Plan and study related reports, Investigator's Brochure/Report of Prior Investigation Summary
- All case report forms and supporting documentation submitted by investigator, samples of Informed Consent Forms, and other information provided to the subjects
- Copies of all IRB/EC approval letters and relevant IRB/EC correspondence and IRB/EC voting list/roster/letter of assurance
- Names of the institutions in which the clinical investigation will be conducted

- Regulatory authorities correspondence, notification and approval, as required by national legislation
- Insurance certificates
- Randomization List
- Names/contact addresses of monitors
- Monitoring visit reports and follow-up letters
- Forms for reporting any adverse events and adverse device effects
- Statistical analyses and underlying supporting data.
- Final report of the clinical investigation
- Study training records for center personnel and Medtronic personnel involved in the study
- Any other records that local regulatory agencies require to be maintained

17.7.4. Sponsor Reports

Medtronic shall prepare and submit the following complete, accurate, and timely reports listed in the tables below (by geography). In addition to the reports listed below, Medtronic shall, upon request of reviewing IRB/EC, regulatory agency or FDA, provide accurate, complete and current information about any aspect of the investigation. Safety data reporting requirements are listed in the adverse event section.

Table 12: Sponsor Reports for the United States

Report	Submit to	Description/Constraints
Withdrawal of IRB/EC approval	Investigators, IRB/EC, FDA, and relevant authorities	Notification within five working days. (21 CFR 812.150(b)(2))
Withdrawal of FDA approval	Investigators, IRB/EC, and relevant authorities	Notification within 5 working days. (21 CFR 812.150(b)(3))
Investigator List	FDA	Submit at 6-month intervals, a current list of the names and addresses of all Investigators participating in the investigation. (21 CFR 812.150(b)(4))
Progress Reports	IRB/EC and FDA	Progress reports will be submitted at least annually. (21 CFR 812.150(b)(5), 812.36(f)
Recall and device disposition	Investigators, Head of Institution, IRB/EC, relevant authorities, and FDA	Notification within 30 working days and will include the reasons for any request that an Investigator return, repair, or otherwise dispose of any devices. (21 CFR 812.150(b)(6))
Failure to obtain Informed Consent Form	FDA	Investigator's report will be submitted to FDA within five working days of notification. (21 CFR 812.150(b)(8))

Report	Submit to	Description/Constraints
Final report	Investigators, IRB/EC, Regulatory authorities upon request, and FDA	Medtronic will notify FDA within 30 working days of the completion or termination of the investigation. A final report will be submitted to the FDA, investigators, and IRBs within 6 months after completion or termination of this study. (21 CFR 812.150(b)(7))
Study deviation	Investigators	Ensure that all deviations from the clinical investigation plan are reviewed with the appropriate clinical investigator(s), are reported on the case report forms and the final report of the clinical investigation. Site specific study deviations will be submitted to investigators periodically.
Other	IRB/EC, and FDA	Accurate, complete, and current information about any aspect of the investigation. (21 CFR 812.150(b)(10))

Table 13: Sponsor reports for Europe

Report	Submit to	Description/Constraints
Premature termination or suspension of the clinical investigation	Investigators, IRB/EC, relevant authorities, and Head of the Institution	Provide prompt notification of termination or suspension and reason(s). (ISO 14155:2011)
Withdrawal of IRB/EC approval	Investigators, IRB/EC, Head of the Institution and relevant authorities	Investigators, IRBs/ECs will be notified only if required by local laws or by the IRB/EC.
Withdrawal of CA approval	Investigators, Head of the Institution, IRB/EC, and relevant authorities	Investigators, IRBs/ECs will be notified only if required by local laws or by the IRB/EC.
Progress Reports	IRB/EC and Regulatory authorities	Will be submitted to the IRB/EC only if required by the IRB/EC.

Report	Submit to	Description/Constraints
Final report	Investigators, IRB/EC and Regulatory authorities, upon request	For centers complying with ISO 14155: • The Investigator shall have the opportunity to review and comment on the final report. • If a clinical Investigator does not agree with the final report, his/her comments shall be communicated to the other Investigator(s). • The coordinating Investigators shall sign the report. If no coordinating Investigator is appointed, then the signature of the Principal Investigator in each center should be obtained. (ISO 14155:2011)
Study deviation	Investigators	Ensure that all deviations from the CIP are reviewed with the appropriate clinical Investigator(s), are reported on the case report forms and the final report of the clinical investigation. (ISO 14155:2011) Center specific study deviations will be submitted to investigators periodically.

Medtronic records and reports will be maintained in a password protected document management system, and paper documents (where applicable) will be stored in secured file cabinets at Medtronic during the course of the study.

After closure of the study, Medtronic will archive records and reports indefinitely.

17.8. Publication and Use of Information

Publications from the STOP AF First study will be handled according to applicable Medtronic standard operating procedures and as indicated in the clinical trial agreement.

Publication Committee

Medtronic may form a publication committee comprised of study Investigators. Medtronic personnel may serve as members of the committee. This committee will manage study publications with the goal of publishing findings from the data. The publication committee will develop the final publication plan as a separate document.

The publication committee's role is to:

- Manage elements addressed in the publication plan,
- Develop the final publication plan under separate cover,
- Execute the publication plan,
- Oversee the publication of primary, secondary [redacted] study results,
- Review and prioritize publication proposals,
- Provide input on publication content,
- Determine authorship,
- Ensure the International Committee of Medical Journal Editors (ICMJE) quality and rules guidance is used, and
- Determine procedure for documentation of decisions related to the generation of publications.

In addition, the committee will apply and reinforce the authorship guidelines set forth in the publication plan. Membership in the publication committee does not guarantee authorship. The committee will meet at as needed.

17.8.1. Management of Primary, Secondary and Ancillary Publications

The publication committee reviews, prioritizes, and manages all publications including primary, secondary and ancillary publications. Primary and secondary publications are those that address analyses of any or all primary objectives or secondary objectives, respectively, as specified in the clinical investigation plan.

An ancillary publication is any publication that does not address the study objectives identified in the clinical investigation plan. They include publications proposed and developed by other Medtronic departments or entities, clinicians participating in this clinical study, and clinicians not participating in this clinical study. The committee will work with Medtronic to ensure that requests do not present conflicts with other proposals, are not duplicative, and to determine which ancillary publication proposals, if any, will be supported.

The committee may decide that no publications, including abstracts, will be published prior to the end of the study or with individual center data. Requests for publications on study objectives utilizing subset data (e.g., regional) will be evaluated for scientific validity and the ability of Medtronic to provide resources.

17.8.2. Criteria for Determining Authorship

Publications will adhere to authorship criteria defined by the International Committee of Medical Journal Editors (ICMJE, Uniform requirements for manuscripts submitted to biomedical journals, www.icmje.org). Individual authorship criteria defined by the target journal or conference will be followed when it differs from ICMJE criteria.

Decisions regarding authorship and contributor-ship will be made by the committee. The selected authors will be responsible for drafting the publication. All selected authors must fulfill the authorship conditions stated above to be listed as authors, and all contributors who fulfill the conditions must be listed as authors.

All investigators not listed as co-authors will be acknowledged as the "STOP AF First Study Investigators" and will be individually listed according to the guidelines of the applicable scientific journal when possible and affiliation. Any other contributors will be acknowledged by name with their specific contribution indicated.

17.8.3. Transparency

Transparency of study results will be maintained by the following means:

- A final report, describing the results of all objectives and analysis, will be distributed to all investigators and IRBs
- Registering and posting the study results on ClinicalTrials.gov based on the posting rules stipulated
- Submitting for publication the primary study results after the study ends
- Disclosing conflicts of interest (e.g., financial) of the co-authors of publications according to the policies set forth by the corresponding journals and conferences
- Making an individual center's study data accessible to the corresponding investigator after the completion of the study, if requested

17.9. Suspension or Early Termination

17.9.1. Planned Study Closure

Study closure is a process initiated by distribution of a study closure letter. Study closure is defined as closure of a clinical study that occurs when Medtronic and/or regulatory requirements have been satisfied per the CIP and/or by a decision by Medtronic or regulatory authority, whichever occurs first. The study closure process is complete upon distribution of the final report or after final payments, whichever occurs last. Ongoing IRB/EC oversight is required until the overall study closure process is complete. Refer to sections 11.5.13 and 11.10 for additional information regarding study exit procedures.

17.9.2. Early Termination or Suspension

Early termination is the closure of a clinical study that occurs prior to meeting defined endpoints. This is possible for the whole study or a single site. Study suspension is a temporary postponement of study activities related to enrollment. This is possible for the whole study or a single site.

17.9.3. Study-wide termination or suspension

Possible reasons for considering study suspension or termination of the study include but are not limited to:

- Decision by Medtronic or regulatory body (where the study is operating under regulatory body authority)
- Adverse events associated with the system or product under investigation which might endanger the safety or welfare of the subject
- Observed/suspected performance different from the product's design intent
- Enrollment is slower than anticipated

17.9.4. Site termination or suspension

Possible reasons for clinical investigator or site termination or suspension include but are not limited to:

- Failure to obtain initial IRB approval or annual renewal of the study
- Persistent non-compliance to the clinical investigation

- Lack of enrollment
- Noncompliance to regulations and the terms of the CTA (e.g. failure to submit data in a timely manner, failure to follow-up on data queries and monitoring findings in a timely manner)
- IRB/EC suspension of the site
- Fraud or fraudulent misconduct is discovered (as defined by local law and regulations)
- Investigator request (e.g., no longer able to support the study)

17.9.5. Procedures for Termination or Suspension

17.9.5.1. Medtronic-initiated and regulatory authority-initiated

- Medtronic will promptly inform the clinical investigators of the termination or suspension and the reasons and inform the regulatory authority where required
- In the case of study termination or suspension for reasons other than a temporary IRB/EC approval lapse, the investigator will promptly inform the IRB/EC and the institution (where required per regulatory requirements)
- In the case of study termination, the investigator must inform the subjects (or legally authorized designees or guardians, US ONLY), and may inform the personal physician of the subjects to ensure appropriate care and follow-up is provided
- In the case of a study suspension, subject enrollment must stop until the suspension is lifted by Medtronic
- In the case of study suspension, enrolled subjects should continue to be followed out of consideration of their safety, rights and welfare

17.9.5.2. Investigator-initiated

- The Investigator will inform Medtronic and provide a detailed written explanation of the termination or suspension
- The Investigator will promptly inform the institution (where required per regulatory requirements)
- The Investigator will promptly inform the IRB/EC and regulatory authority (where required per regulatory requirements)
- The Investigator will promptly inform the subjects, and may inform personal physician of the subjects to ensure appropriate care and follow-up is provided
- In the case of study suspension, enrolled subjects should continue to be followed out of consideration of their safety, rights and welfare

17.9.5.3. IRB/EC-initiated

- The Investigator will inform Medtronic and provide a detailed written explanation of the termination or suspension within 5 business days
- Subject enrollment must stop until the suspension is lifted
- Subjects already enrolled should continue to be followed in accordance with IRB policy or its determination that an overriding safety concern or ethical issue is involved
- The Investigator will inform his/her institution (where required per local requirements)

- The Investigator will promptly inform the subjects (or legally authorized designees or guardians, except in Europe), and may inform the personal physician of the subjects, with the rationale for the study termination or suspension
- The Investigator will inform local regulatory authority, where required per regulatory requirements

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19. Appendices

Appendix A: CRYOBALLOON SAFETY DATA LITERATURE SEARCH

The following pertains to Medtronic cryoablation products and/or related devices and includes reports identified in the scientific literature that were published from June 14, 2005 to March 15, 2015.

Search Methodology

Three literature searches were conducted in the following databases to ensure comprehensive coverage of globally published clinical evidence for medical device products and therapies. All searches were conducted in the STN database platform.

EMBASE, published by Elsevier, contains over 11 million records with over 500,000 citations added annually. EMBASE's international journal collection contains over 5,000 biomedical journals from 70 countries.

MEDLINE is the U.S. National Library of Medicine's premier bibliographic database covering the fields of medicine, nursing, dentistry, veterinary medicine, the health care system, and the preclinical sciences. MEDLINE contains bibliographic citations and author abstracts from more than 5,000 biomedical journals published in the United States and 80 other countries. The database contains over 15 million citations.

Search Results

Search #1 – Medtronic Cryocath Arctic Front Brands and Models

A search was conducted for the Medtronic Cryocath Arctic Front brands and models as outlined in the table below. The search was limited to English language, human only, clinical trials, case reports, registries, editorials or meta analyses for the time period of June 14, 2005 to March 15, 2015. All notes, comments, letters, books, conference papers, practice guidelines and patents were removed from the search results. A total of 56 unique articles were located. Note that as Arctic Front Advance ST was not released to the market at the time of this search it was not included as a search term.

Literature Search Specifications

Search Terms	(MEDTRONIC OR ARCTIC()FRONT) AND (ARCTIC()FRONT OR 2AF231 OR 2AF281 OR 2AF232 OR 2AF282) **LIMITED TO:** **Study Types:** clinical trials, meta analyses, case reports, registries, editorials
Databases Searched	MEDLINE, EMBASE
Specified Timeframe	June 14, 2005 – March 15, 2015

Search #2 – Medtronic Cryocath Arctic Front Advance Brands and Models

A search was conducted for the Medtronic Cryocath Arctic Front Advance brands and models as outlined in the table below. The search was limited to English language, human only, clinical trials, case reports,

registries, editorials or meta-analyses for the time period of June 14, 2005 to March 15, 2015. All notes, comments, letters, books, conference papers, practice guidelines and patents were removed from the search results. A total of 14 unique articles were located for this search.

Literature Search Specifications

Search Terms	(MEDTRONIC OR ARCTIC()FRONT()ADVANCE) AND (ARCTIC()FRONT()ADVANCE OR 2AF234 OR 2AF284 OR 2AF283 OR 2AF233) **LIMITED TO:** **Study Types:** clinical trials, meta analyses, case reports, registries, editorials
Databases Searched	MEDLINE, EMBASE
Specified Timeframe	June 14, 2005 – March 15, 2015

Search #3 – Cryoballoon Literature

A search was conducted for industry-wide literature on cryoballoons. The search was limited to English language, human only, clinical trials, case reports, registries, editorials or meta-analyses for the time period of June 14, 2005 to March 15, 2015. All notes, comments, letters, books, conference papers, practice guidelines and patents were removed from the search results. A total of 173 unique articles were located.

Literature Search Specifications

Search Terms	CRYOBALLOON OR CRYOBALLOONS **LIMITED TO:** **Study Types:** clinical trials, meta analyses, case reports, registries, editorials
Databases Searched	MEDLINE, EMBASE
Specified Timeframe	June 14, 2005 to March 15, 2015

Final Result

Results from Search #1, Search #2 and Search #3 were combined and duplicates were removed. A total of 182 unique articles were located. Of these 182 articles, 54 articles were excluded per the following:

- 2 editorials
- 7 reviews with no new specific information
- 3 duplicates within the search
- 1 expert consensus statement
- 2 meta-analyses
- 3 were study design papers with no results
- 1 case report with no adverse events reported
- 6 did not include the Arctic Front or Arctic Front Advance cryoballoon or Atrial Fibrillation
- 4 abstracts only (unable to access full article) with no new information
- 25 articles were excluded as they did not report safety

Additional articles Medtronic was aware of or that were published after the searches were conducted were included.

Appendix B: DRAFT DATA COLLECTION ELEMENTS (CASE REPORT FORMS)

Draft Case Report Forms for the STOP AF First study will be provided under separate cover. Final CRFs will be provided to study centers via the electronic data management system after the center has fulfilled all requirements for database access.

Appendix C: INFORMED CONSENT FORM TEMPLATE

The Informed Consent Form Template will be distributed under separate cover.

Appendix D: PARTICIPATING INVESTIGATOR AND INSTITUTIONS

A list of participating Investigators and institutions will be distributed under separate cover.

Appendix E: IRB LIST

A final IRB list will be distributed under separate cover.

Appendix F: FORESEEABLE ADVERSE EVENTS

The information provided in this section pertains to foreseeable adverse events that may be observed in study subjects and may collectively assist in identifying those events for a given device or therapy that are unexpected in nature. The foreseeable adverse events information consists of two parts: a listing of potential adverse events associated with cryoablation therapy/procedure and adverse event rates reported in published literature for same therapy/procedure (see Appendix A). An evaluation of potentially anticipated events and reported events in literature may be used in combination with device labeling/IFU, current event reporting information, and other published data to assess for an unexpected occurrence.

The cryoablation procedure involves surgery, therefore, standard adverse events associated with a surgical procedure may be experienced (e.g. anesthesia complications, injury, infections, bleeding, exacerbation of pre-existing conditions, healing complications, etc.). The focus of this section is to specifically address in more detail, those events that are foreseeable due to the use, performance, and/or presence of the Arctic Front Advance™ CryoAblation Catheter under investigation.

Additional potential risks associated with the Arctic Front Advance™ CryoAblation Catheter, as well as risk minimization are discussed within section 12.

Treatment required for procedure and/or cryoablation system related adverse events that are experienced may include medication or other surgical and medical remedies. The adverse events associated with the use of the Arctic Front Advance™ CryoAblation Catheter include but are not limited to those in Table 14 and Table 15.

Table 14 pertains to the foreseeable/anticipated adverse events that may be observed in the study and may assist in identifying those adverse events that are unexpected in nature.

Table 14: Foreseeable Adverse Events

Anemia	Feeling cold	Pseudoaneurysm
Anxiety	Fever	Pulmonary edema
Arrhythmia	Gastrointestinal discomfort	Pulmonary embolism
Arteriovenous fistula	Gastroparesis	Pulmonary hemorrhage
Atrial fibrillation	Headache	Pulmonary hypertension
Atrial flutter	Heart block	Pulmonary infarction
Atrio-esophageal fistula	Heart failure	Pulmonary infiltration
Back pain	Hematemesis	Pulmonary vein

		stenosis
Bleeding	Hematoma	Renal impairment
Blurred vision	Hemoptysis	Respiratory arrest or pulmonary arrest
Bronchial fistula	Hemothorax	Right bundle branch block
Bronchitis	Hiccups	Shivering
Bruising	Hypertension	Shortness of breath
Cardiac arrest or cardiopulmonary arrest	Hypotension	Sore throat
Cardiac perforation or cardiac vein perforation or perforation of surrounding tissue	Hypoxia	ST segment elevation
Cardiac tamponade	Injury to pulmonary vein e.g. pulmonary vein dissection, pulmonary vein hematoma	Stroke or cerebrovascular accident
Cerebral embolism	Lightheadedness	Syncope
Chest discomfort or pain or pressure	Lung injury	Tachycardia
Coronary artery spasm	Myocardial infarction	Thrombosis or thrombus
Cough	Nausea	Transient ischemic attack
Death	Nerve injury e.g. phrenic nerve injury	Urinary infection
Diarrhea	Neurological impairment	Vascular access site complication

Dizziness	Paralysis or paresis	Vasospasm
Dressler's syndrome	Pericardial effusion or pericardial tamponade	Vasovagal reaction
Dysphagia	Pericarditis	Visual changes or visual impairment
Embolism	Pleural effusion	Vomiting
Esophageal injury/damage (including atrio-esophageal fistula)	Pneumonia	
Fatigue	Pneumothorax or collapse of lung	

Table 15 is a summary of reported procedure and Arctic Front Advance™ Cardiac CryoAblation Catheter related adverse events reported in a Medtronic Clinical Evaluation Report for The Arctic Front Family of Catheters Recertification (Rev 1A, 19MAY2015). The observed rate is based on the study populations that included a total of 11,242 patients.

Table 15: Arctic Front and Arctic Front Advance™ Complications Reported in Literate for Paroxysmal and Persistent AF Patients

Events	N=11,242 Rate (95% CI*)
Transient phrenic nerve injury (resolved prior to procedure end)	4.26% (3.89-4.65%)
Phrenic nerve injury	2.18% (1.92-2.47%
Groin hematoma	0.58% (0.45-0.74%)
Pericardial effusion/pericardial tamponade	0.53% (0.41-0.69%)
Pseudoaneurysm	0.36% (0.25-0.48%)
Hemoptysis	0.27% (0.18-0.38%)
Femoral arterio-venous fistula	0.21% (0.14-0.32%)

Events	N=11,242 Rate (95% CI*)
Cardiac tamponade	0.20% (0.13-0.31%)
Bleeding	0.14% (0.08-0.23%)
Gastroparesis	0.14% (0.08-0.23%)
Hematoma	0.14% (0.08-0.23%)
Atrial flutter	0.13% (0.07-0.22%)
Atrial tachycardia	0.12% (0.06-0.20%)
Esophageal damage/ulceration	0.12% (0.06-0.20%)
Transient ischemic attack	0.12% (0.06-0.20%)
Stroke or cerebral vascular accident	0.10% (0.05-0.18%)
Myocardial infarction	0.05% (0.02-0.12%)
Atrio-esophageal fistula	0.04% (0.01-0.10%)
Guidewire dissection	0.04% (0.01-0.10%)
Pulmonary vein stenosis	0.04% (0.01-0.10%)
ST elevation	0.04% (0.01-0.10%)
Accidental femoral artery puncture	0.03% (0.01-0.09%)
Inguinal aneurysm	0.03% (0.01-0.09%)
Pulmonary edema	0.03% (0.01-0.09%)
Difficulty swallowing/dysphagia	0.02% (0.002-0.06%)
Hemothorax	0.02% (0.002-0.06%)
Pericarditis	0.02% (0.002-0.06%)

Events	N=11,242 Rate (95% CI*)
Pulmonary vein hematoma	0.02% (0.002-0.06%)
Thrombosis or thrombus	0.02% (0.002-0.06%)
Vasovagal reaction	0.02% (0.002-0.06%)
Chest discomfort or pain or pressure	0.01% (0.0002-0.5%)
Cough	0.01% (0.0002-0.5%)
Death	0.01% (0.0002-0.5%)
Headache	0.01% (0.0002-0.5%)
Hemoptysis-clinically important	0.01% (0.0002-0.5%)
Inappropriate sinus tachycardia	0.01% (0.0002-0.5%)
Lightheadedness	0.01% (0.0002-0.5%)
Nausea	0.01% (0.0002-0.5%)
Odynophagia	0.01% (0.0002-0.5%)
Pneumonia	0.01% (0.0002-0.5%)
Pneumothorax or collapsed lung	0.01% (0.0002-0.5%)
Pulmonary infarction	0.01% (0.0002-0.5%)
Pulmonary infiltration	0.01% (0.0002-0.5%)
Sinus arrest/3rd degree AV block	0.01% (0.0002-0.5%)
Transient AV block	0.01% (0.0002-0.5%)

*95% CI calculated with binomial exact methods

Appendix G: PRE-CLINICAL TESTING

A summary of results from pre-clinical testing with the Arctic Front Advance™ Cardiac CryoAblation Catheter is provided in the Report of Prior Investigations Summary.